Synthetic Approaches to the Neuraminidase Inhibitors Zanamivir (Relenza) and Oseltamivir Phosphate (Tamiflu) for the Treatment of Influenza

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1. Introduction

Influenza, a severe viral infection of the respiratory system, is responsible for a significant morbidity and mortality due to both annual epidemics and unpredictable pandemics. In the United States alone, $10-20\%$ of the population is affected every year, which results in approximately 110,000 hospitalizations and more than 20,000 deaths with an estimated cost of U.S. $12 billion.[1] In addition to the annual occurrence of the disease, there is a growing concern that a worldwide pandemic will inevitably happen within the next few years. Since the 1500s, the world has seen 22 influenza pandemics,

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one every 25 years on average. The most recent ones in the 20th century were the Spanish flu (1918), which killed 20−50 million people worldwide, the Asian flu (1957, 1−2 million casualties), the Hong Kong flu (1968, approximately 700,000 casualties), and the Russian flu (1977).[2] It is estimated that if a similar event took place today, about 30% of the world's population could die.

The primary method of influenza prevention is through vaccination.[3] The time required to produce enough vaccine to immunize a large percentage of the population is 6−8 months, and it can only be stockpiled for 18 months. In addition, it should be administered at least four weeks before becoming in contact with the virus to be effective. However, the virus mutates from season to season and this translates into the need to produce a new vaccine every year. Due to the lack of effectiveness of a newly produced vaccine over prolonged periods of time, this form of immunization would fail to combat an influenza pandemic. As an alternative to vaccination, antiviral drugs and neuraminidase inhibitors can also be employed to combat influenza.

Several molecular entities on the virus envelope have been identified as potential targets for drug interaction, namely the M2 protein, haemagglutinin, and neuraminidase (sialidase).[4] The M2 protein is an ion channel on the lipid envelope of the virus that controls the pH-dependent release of ribonucleoproteins, which causes virus uncoating.[5] Haemagglutinin is a surface glycoprotein that is responsible for initiating the infection through binding to the terminal sialic acid (**1**, Figure 1) residues on the cell membrane of the
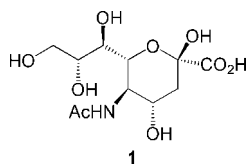

Figure 1. Structure of sialic acid (*N*-acetylneuraminic acid).

respiratory tract. It then induces the cell to accept the virus, and the replication process starts. Neuraminidase is also a surface glycoprotein that cleaves sialic acid residues from

the newly created virions to avoid virion aggregation, which would otherwise render them ineffective to invade new cells. In addition, this protein also facilitates the spreading of the virus through the mucus of the respiratory tract.[6] Therefore, a drug that is designed to bind and block the active site of this protein could become an efficient treatment against the disease.

The M2 inhibitors amantadine HCl (**2**) and rimantadine HCl (**3**) were the first two antiviral drugs approved for the treatment and prophylaxis of influenza A (Figure 2). The
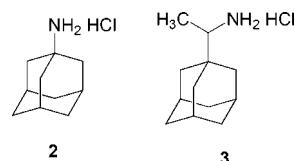
Figure 2. Structures of amantadine HCl (**2**) and rimantadine HCl (**3**).

mechanism of action is through the blockage of viral uncoating, but their use has been limited due to their severe CNS side effects,[7] the rapid emergence of resistance in viral strains,[8] and the lack of efficacy against influenza B virus, which does not express the M2 protein.[5a] In addition, these drugs are only effective if the treatment is initiated within the first 48 h after the symptoms are identified.[5] Their specific activity against the influenza A virus has been attributed to an ion channel blocking of a specific viral protein.

More recently, the focus has been on the inhibition of neuraminidase, since this protein plays a fundamental role in the elution of the newly created virions from infected cells. The first example of this type of compounds is 2-deoxy-2,3-dehydro-*N*-acetylneuraminic acid (DANA, **4**, Figure 3), which was first reported in 1974.[9] The application of structure-based drug design as well as the determination of the X-ray crystal structure of neuraminidases A and B and their complexes with sialic acid in the early 1980s[10] helped determine the binding interactions between the functional groups and the active site. This development led to the design of far more potent inhibitors by replacing the hydroxyl group at the four position of the ring with more basic groups such as amino or guanidino. As a consequence, zanamivir (**5**) and oseltamivir (**6**) were discovered and, to date, they are the only two drugs approved in this category to combat both influenza A and B (Figure 3).

Both zanamivir and oseltamivir are structurally similar to sialic acid, and they were designed as analogues of oxocarbonium intermediate **9** to mimic the transition state of the proposed mechanism for the enzymatic hydrolysis of sialylglycosides (Scheme 1) to give sialic acid (**1**).[11b] The competitive blocking of neuraminidase prevents sialic acid cleavage, and as a result, the viral release and subsequent spread are inhibited.

The discovery and development of antiinfluenza drugs is a very active area of research, and the recent synthetic progress has been reported in a number of reviews.[11] This article will exclusively focus on zanamivir and oseltamivir due to their preeminent role to treat the condition, and it intends to provide a comprehensive and updated overview on the syntheses of these two commercially available drugs, from their inception until the most recent approaches published in the literature.
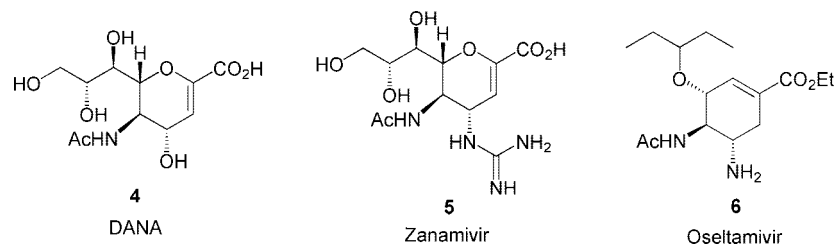
Figure 3. Structures of DANA (**4**), zanamivir (**5**), and oseltamivir (**6**).

Scheme 1. Proposed Mechanism for the Enzymatic Hydrolysis of Sialylglycosides

2. Synthetic Approaches to Zanamivir

2.1. Introduction

Zanamivir (**5**, Relenza) was the first neuraminidase inhibitor to be synthesized based on rational drug design.[12] The drug was discovered in 1989 by Biota scientists in conjunction with Australia's Commonwealth Scientific and Industrial Research Organization (CSIRO) and the Victorian College of Pharmacy at Monash University. The molecule was licensed to GlaxoSmithKl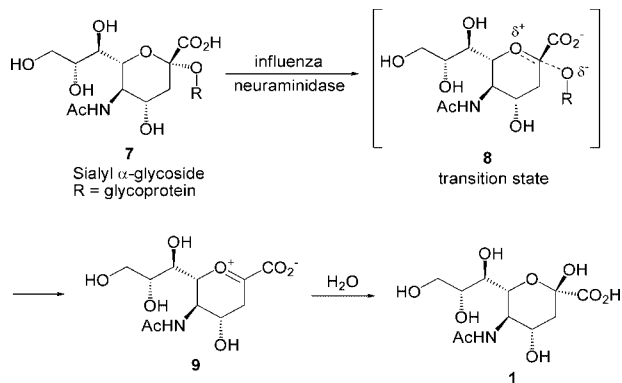ine in 1990 for clinical development and approved by the FDA for commercialization in the United States in 1999. Zanamivir is a micronized, dry powder combined with lactose as the principal base that is highly effective against influenza A and B. Due to its poor oral bioavailability (2−3%), it must be administered topically to the respiratory tract by intranasal spray or by inhalation at a dose of 10 mg twice a day for five days. The evaluation of zanamivir in the treatment of influenza[4c,13] as well as its preparation[11b,e] has been reported in several articles.

2.2. First Synthesis of Zanamivir at Monash University

Zanamivir was first reported by researchers at Monash University in Australia. The synthetic route that they described is shown in Scheme 2.[14] Methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-2,6-anhydro-3,5-dideoxy-D-*glycero*-D-*galacto*-non-2-enonate (Neu4,5,7,8,9Ac$_5$2en1Me, **10**),[15] which can be prepared from NANA in several steps,[16] was treated with BF$_3$·OEt$_2$ to give allylic oxazoline **11**, which is susceptible to nucleophilic attack by azide (either as lithium azide or azidotrimethylsilane) to provide intermediate **12**. This method gave the expected inversion product with very good stereoselective control even on a multigram scale. Hydrogenation of **12** at atmospheric pressure in the presence of 10% Pd/C afforded amine **13**. The hydrogenation conditions were carefully chosen to avoid undesired side reactions such as acetate migration or double bond reduction. As an alternative, azide reduction with Ph$_3$P[16] gave a considerably lower yield. Ester hydrolysis with Amberlite-IRA 400 (OH$^-$) resin and aqueous sodium hydroxide followed by neutralization with Dowex-50W × 8 (H$^+$) provided sodium salt **14**. The completion of the synthesis was accomplished through the reaction of **14** with aminoiminomethanesulfonic acid (**15**)[17] to give zanamivir (**5**).

This first preparation of zanamivir represents a historic landmark in the pursuit of neuraminidase inhibitors, since it was the first disclosure in the literature of a member of this new class of drugs that, eventually, would become an effective treatment against influenza A and B. It starts from an advanced intermediate (**10**), which will add synthetic steps to the overall process from more readily available materials. This medicinal chemistry approach only produced milligram quantities of the drug and employed unsafe reagents such as LiN$_3$ and techniques such as chromatography and lyophilization for intermediate isolation, which would preclude it from becoming a practical synthesis on scale. The

Scheme 2. First Synthesis of Zanamivir at Monash University
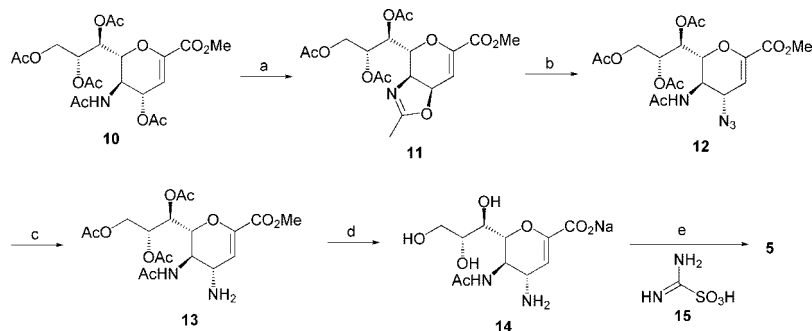
Reagents and conditions: (a) BF$_3$·Et$_2$O, MeOH/CH$_2$Cl$_2$, 25-30 °C, 16 h, 96%. (b) Me$_3$SiN$_3$, *tert*-BuOH, 80 °C, 4 h, 82.5%. (c) H$_2$, Pd/C (10%), AcOH/MeOH/toluene, 1 atm., 1 h, 72%. (d) (i) Amberlite IRA-400 (OH$^-$), MeOH, rt, 3 h; (ii) Dowex-50W X 8 (H$^+$), 91.6%. (e) **15**, H$_2$O, K$_2$CO$_3$, 30-40 °C, 18 h, 57%.

Scheme 3. Synthesis of Zanamivir from Acetylneuraminic Acid (1) by the Merck Frosst Centre
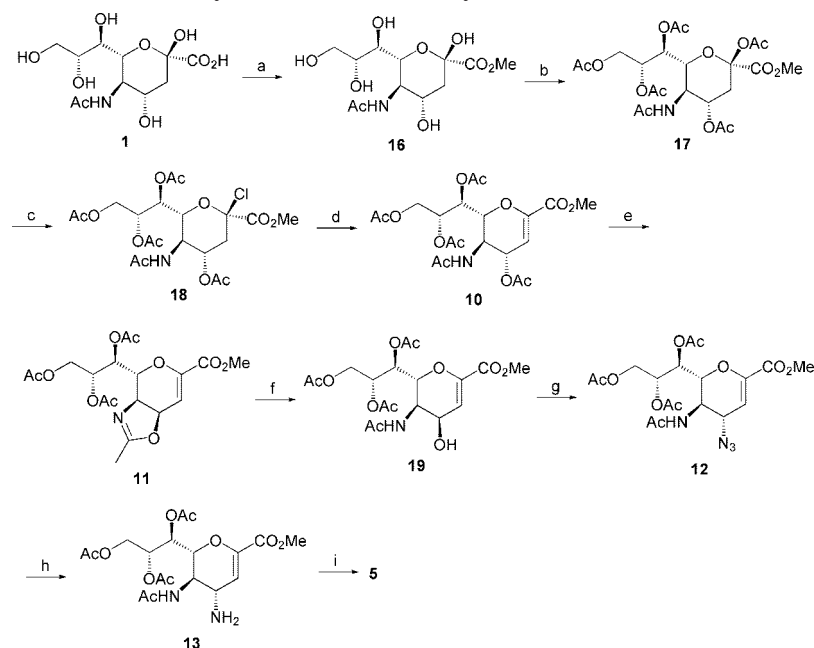
Reagents and conditions: (a) H$^+$ resin, MeOH, rt, 18 h. (b) AcCl, rt, 48 h. (c) AcCl, HCl gas, -42°C, 20 h. (d) DBU, PhH, rt, 3 h, 73% (4 steps). (e) BF$_3$•OEt$_2$, PhH/MeOH, 5 °C to rt, 18 h, 42%. (f) HOAc/H$_2$O, EtOAc, rt, 16 h, 42%. (g) DPPA, DBU, PhH, 5 °C to rt, 23 h, 87%. (h) H$_2$S, py, rt, 1.5 h, 78%. (i) (i) 1*H*-pyrazole-1-carboximidine HCl, DIPEA, DMF, rt, 48 h; (ii) NaOH, H$_2$O/MeOH, rt, 18 h; (iii) AcOH, 54%.

availability of NANA in large quantities and cost may also be another limitation.

2.3. Synthesis of Zanamivir from *N*-Acetylneuraminic Acid (NANA) by the Merck Frosst Centre

Researchers at the Merck Frosst Centre in Canada utilized commercially available *N*-acetylneuraminic acid (NANA, **1**) as the starting material to develop a reproducible synthesis of intermediate **19** en route to zanamivir (Scheme 3).[18] Another goal of this work was to avoid the use of azidotrimethylsilane to introduce the azido group, since this reagent generates potentially explosive hydrazoic acid. This synthetic route proceeds through several of the intermediates reported in the previous synthesis. Thus, *N*-acetylneuraminic acid (NANA, **1**) was esterified in dry methanol with a cation-exchange resin as catalyst to generate methyl ester **16**.[19] Acetylation of all the free hydroxy groups[20] followed by displacement of the 2-acetoxy group by chloride[21] in a pressurized vessel afforded pentaacetylated intermediate **18**. The elimination step to produce unsaturated ester **10** was carried out with DBU as base.[22] The complete removal of the acetic acid generated in the chlorination step was crucial to provide a good yield of the elimination product, or otherwise, mixtures of **10** and **17** were obtained. The relative stereochemistry between the acetoxy and acetamido groups at carbons 4 and 5 of **10**, respectively, was determined by analyzing the value of the coupling constant (J (4, 5) = 8.3 Hz), which indicated a pseudo-*trans* relationship. The epimerization of the 4α-center was carried out through oxazoline **11**.[23] Early attempts to prepare azide **12** *via* the formation of a sulfonate or mixed anhydride resulted in decomposition. Finally, **12** was successfully prepared by an alternative to the Mitsunobu-type conditions that involved the use of diphenylphosphoryl azide (D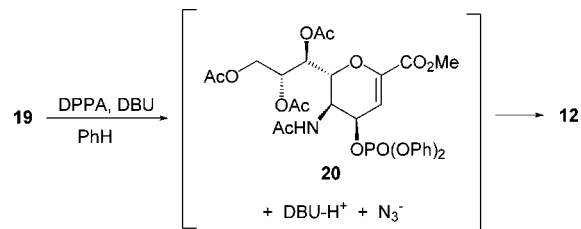PPA).[24] This was the first time that such a process, shown in detail in Scheme 4, was applied to a sugar. The reaction seemed to be completely

Scheme 4. Stereoselective Conversion of Alcohol 19 to Azide 12 through the Use of DPPA

stereoselective, since the presence of the other stereoisomer could not be detected by ^{1}H NMR. The azido group was reduced with H$_2$S in pyridine to give amine **13**.[23] The introduction of a guanidine group as the last step of the synthesis was first attempted through the use of either 3,5-dimethyl-1-guanylpyrazole nitrate or *S*-methylisothiouronium sulfate[23,25] without success. This transformation was finally accomplished with 1*H*-pyrazole-1-carboximidine HCl.[26] Attempts at trying to convert alcohol **19** to zanamivir under Mitsunobu conditions using *N*,*N*′-bis(*tert*-butyloxycarbonyl)guanidine[27] were unsuccessful as well.

This high-yielding process was implemented on a milligram scale and describes new approaches for the introduction of the amino group at the carbon 4 position of the ring without resorting to the use of Li or NaN$_3$ and for the synthesis of the guanidino group. The route employs multiple chromatographic purifications and freeze-drying for intermediate and final product isolation, respectively. Most of the intermediates are solids, and this fact brings about the possibility of purification *via* recrystallization to streamline the process and render it amenable to scale.

2.4. Scalable Route to Zanamivir by Glaxo

The first and only preparation of zanamivir on scale to date was undertaken by researchers at Glaxo in the United Kingdom,[28] and it shares some common intermediates with

Scheme 5. Scalable Route to Zanamivir by Glaxo
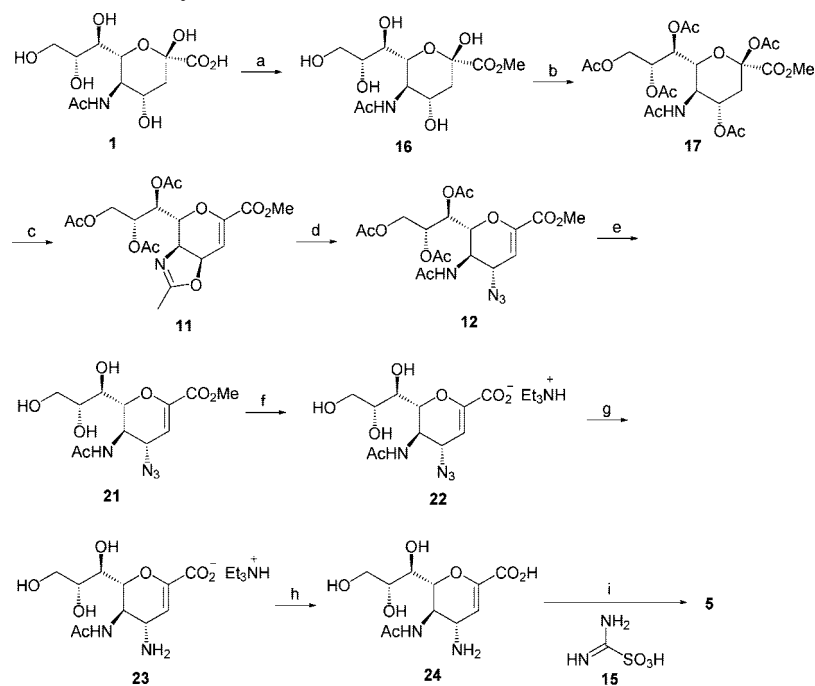
Reagents and conditions: (a) HCl gas, MeOH, 50 °C, 2.5 h, 94%. (b) Ac$_2$O, DMAP, py, 0 °C to rt, 18 h. (c) TMSOTf, EtOAc, 52 °C, 2.5 h, 62% (2 steps). (d) TMSN$_3$, *tert*-BuOH, 80 °C, 10.5 h, 76%. (e) NaOMe, MeOH, rt, 2.5 h, 71%. (f) TEA, H$_2$O, rt, 7 h. (g) H$_2$, Lindlar catalyst, H$_2$O, 21 h. (h) Dowex 2 x 8 (Cl$^-$) resin, 55% (3 steps). (i) **15**, NaOH, K$_2$CO$_3$, H$_2$O, 40 °C, then 20 °C, 16 h, 48%.

the previous two syntheses (Scheme 5). This route also started with *N*-acetylneuraminic acid (NANA, **1**), which was converted to methyl ester **16** with HCl gas as catalyst in methanol. The pentaacetoxy intermediate **17** was prepared by treating **16** with excess acetic anhydride and DMAP as catalyst. These conditions gave clean β-OAc isomer, whereas when HClO$_4$ was used as catalyst, a mixture of α- and β-OAc isomers was obtained. Cyclic oxazoline **11** was obtained through a modification of the method previously described by treating **17** with TMSOTf in warm ethyl acetate.[16] Interestingly, when MeCN was used as solvent, up to 10% of the Ritter product **25** was obtained (Figure 4). TMSN$_3$ in
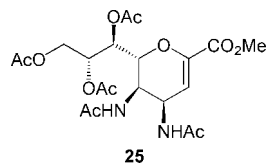
Figure 4. Structure of Ritter byproduct.

hot *tert*-butanol was found superior to convert **11** to azide **12** stereoselectively. This is the point at which the synthetic route diverges from previous approaches. The transformation of the azido group to give rise to the desired amine required reducing conditions that had to leave the double bond unaffected. This was accomplished by first removing the acetate protecting groups with catalytic NaOMe to gain water solubility, followed by hydrolysis of the methyl ester with aqueous TEA to generate triethylammonium salt **22**. This salt was then subjected to hydrogenation in the presence of Lindlar catalyst to give amine **23**, which was desalted using a Dowex 2 × 8 ion-exchange resin to give free amino acid **24**. The use of Pd/C also reduced the double bond. The completion of the synthesis was carried out with aminoimi-nomethanesulfonic acid **15** as before[23] to introduce the

guanidine functionality. Crystalline zanamivir was then isolated by ion-exchange chromatography.

The involvement of the Process Research department at Glaxo allowed for the development of a methodology amenable to scale. Even though only 1.28 g of zanamivir was produced, as reported in this publication, several steps were run on hundreds of grams scale, including the step to introduce the amino group at carbon 4 *via* azide chemistry (600-g scale). Desalting and freeze-drying of one of the intermediates and isolation of zanamivir through ion-exchange chromatography were necessary as purification techniques, but the rest of the intermediates could be isolated by recrystallization. The overall yield for this 9-step synthesis was 8.3%, which should be optimized to improve throughput.

2.5. Synthesis of Zanamivir from D-Glucono-δ-lactone by Yao's Group

A publication from Yao's group at the Chinese Academy of Sciences presented a completely different approach for the preparation of advanced intermediate **12** toward the synthesis of zanamivir (Scheme 6).[29] The authors highlighted the fact that the starting material is cheap D-glucono-δ-lactone **26**, even though at the expense of a long, linear synthetic route. The key steps are a highly diastereoselective allylation of an imine intermediate, a regioselective aziridine-opening step with sodium azide, and chemoselective oxidations of vicinal diols. Imine **27**, prepared by known literature methods,[30] was treated with allylmagnesium bromide in diethyl ether to afford amine **28** as a single diastereomer. Other reagents (propargyl bromide−Zn dust, propargylmagnesium bromide, and allyl bromide−zinc dust), solvents, and temperatures gave less satisfactory results. The stereochemistry of the imine addition was later confirmed by X-ray crystal-lography of azide **34**. Acetylation of **28** followed by

Scheme 6. Preparation of Diol 35 en Route to Advanced Intermediate 12 by Yao's Group
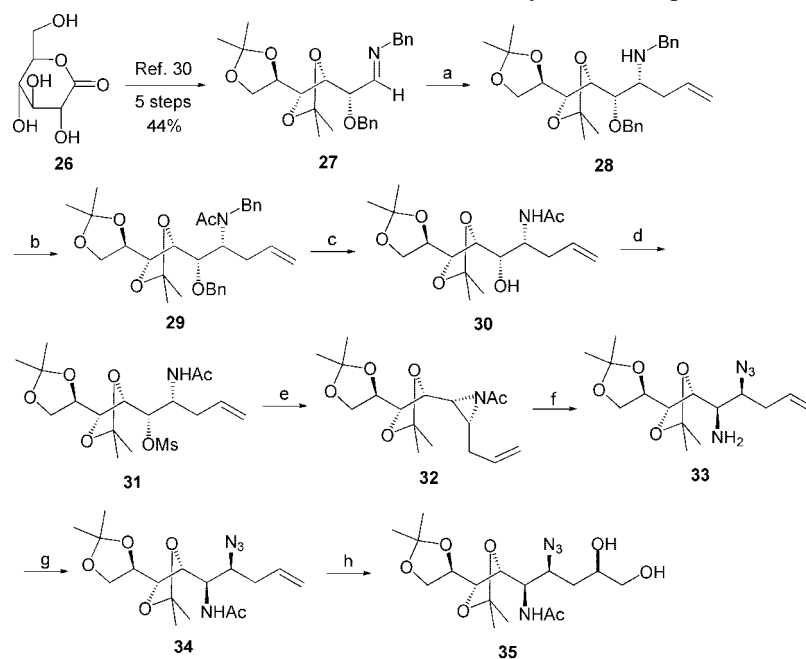
Reagents and conditions: (a) C₃H₅MgBr, Et₂O, 0-25 °C, 56%. (b) Ac₂O, TEA, CH₂Cl₂, 88%. (c) Li, NH₃, THF, -40 °C, 1 h, 82%. (d) MsCl, TEA, CH₂Cl₂, 20 °C, 2 h, 84%. (e) NaH, THF, 40 °C, 24 h, 87%. (f) NaN₃, NH₄Cl, EtOH/H₂O, reflux, 4 h, 62%. (g) Ac₂O, TEA, DMAP, CH₂Cl₂, rt, 30 min, 88%. (h) cat. OsO₄, NMO•H₂O, *tert*-BuOH/acetone/H₂O, rt, 14 h, 96%.
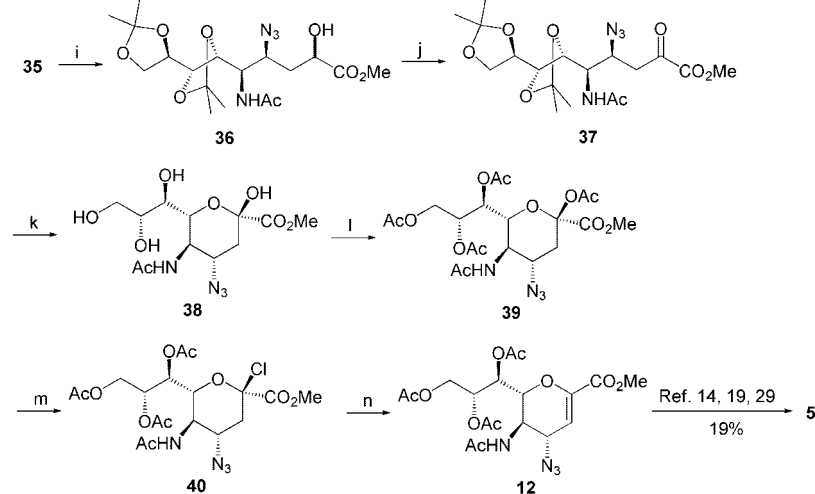
Reagents and conditions: (i) (i) KBr, TEMPO, TBAB, Ca(ClO)₂, 16-20°C. (ii) MeI, K₂CO₃, DMF, 4 h, rt, 80%. (j) DMP, CH₂Cl₂, 0 °C. (k) 40% aq. HF in MeCN (v/v = 1:19), 30 °C, 4 h, 52% (2 steps). (l) Ac₂O, py, 0 °C to rt, 12 h, 65%. (m) HCl, CH₂Cl₂, -40 °C to rt, 14 h, 74%. (n) DBU, CH₂Cl₂, 10 °C, 1 h, 97%.

deprotection of both benzyl groups with Li metal in liquid ammonia provided alcohol **30**. The mesylation of **30** and subsequent treatment with NaH to afford acetylated aziridine **32** set the stage for the introduction of the azide functionality. A number of conditions were tried, such as NaN₃/DMF, LiN₃/DMF, TMSN₃/ZnBr₂, TMSN₃/BF₃•OEt₂, TMSN₃/InBr₃,[31] and TMSN₃/TMSOTf without success. Only NaN₃/NH₄Cl in a EtOH/H₂O mixture at reflux regioselectively opened **32** at the less hindered position to give allylic azide **33**. The acetylation of **33** provided highly crystalline intermediate **34**, whose absolute stereochemistry was unequivocally determined by X-ray analysis. The dihydroxylation of alkene **34** was carried out with catalytic OsO₄ and NMO as co-oxidant to give diol **35**. The primary hydroxyl group of **35** was selectively oxidized with TEMPO/Ca-(ClO)₂[32] (Scheme 6 (bottom)) to afford an acid intermediate that, without isolation, was converted to methyl ester **36** with

MeI. The secondary hydroxyl group in **36** was oxidized with Dess−Martin periodinane to generate α-ketoester **37**. The use of Swern conditions for this oxidation and the chromatographic purification of **37** gave elimination product **41** (Figure 5) after the loss of a molecule of HN₃. The acetonide

Figure 5. Elimination product from the Swern oxidation of alcohol **36**.

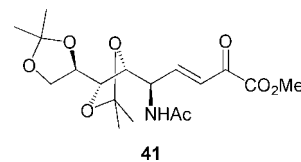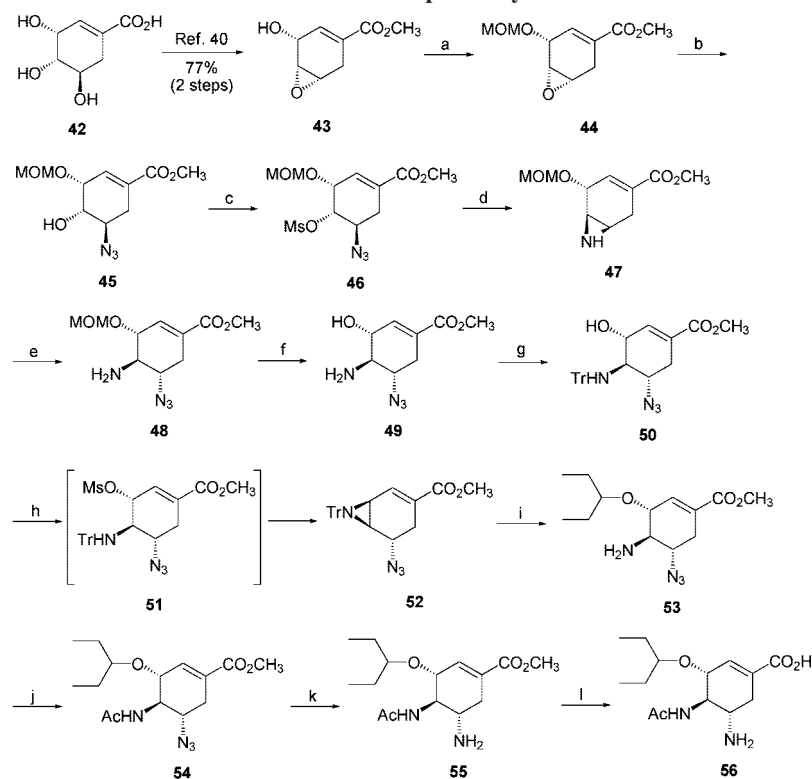groups in crude **37** were cleaved with 40% aqueous HF[33] to provide cyclic intermediate **38**. The synthesis of the target compound **12** was completed *via* the preparation of pen-

Scheme 7. Synthesis of Acid 56 as the First Candidate for Development by Gilead Sciences Inc.

Reagents and conditions: (a) MeOCH₂Cl, DIPEA, CH₂Cl₂, reflux, 3.5 h, 97%. (b) NaN₃, NH₄Cl, MeOH/H₂O, reflux, 15 h, 86%. (c) MeSO₂Cl, TEA, CH₂Cl₂, 0 °C to rt, 15 min, 99%. (d) (i) Ph₃P, THF, 0 °C to rt, 3 h; (ii) TEA, H₂O, rt, 12 h, 78%. (e) NaN₃, NH₄Cl, DMF, 65-70 °C, 21 h, 77%. (f) HCl, MeOH, rt, 4 h, 99%. (g) TrCl, TEA, CH₂Cl₂, 0 °C to rt, 3 h. (h) MeSO₂Cl, TEA, CH₂Cl₂, 0 °C to rt, 22 h, 86% (2 steps). (i) BF₃•OEt₂, 3-pentanol, 70-75 °C, 2 h. (j) Ac₂O, DMAP, pyridine, rt, 18 h, 69% (2 steps). (k) Ph₃P, THF/H₂O, 50 °C, 10 h, 90%. (l) (i) KOH, THF, rt, 40 min; (ii) Dowex 50WX8, 75%.

taacetylated **39** with acetic anhydride,[34] followed by selective displacement of the α-acetoxy group by chloride[35] to give intermediate **40** and HCl elimination in the presence of DBU. The completion of the synthesis of zanamivir (**5**) from **12** has been described in previous approaches.[14,18,28]

This route, unlike the previous ones, builds the cycloxene ring from acyclic intermediates and contains some interesting chemistry, such as the Grignard addition to imine **27** and the regioselectivity displayed in the aziridine-opening by azide. On the other hand, protecting group chemistry is needed on several occasions, which decreases the efficiency of the process, and all the steps were only implemented on milligram scale. Even though the starting material is cheap, D-glucono-δ-lactone, the large number of synthetic steps (24), the use of numerous chromatographic purifications, and the very low overall yield (0.2%) undermine the utility of this route to produce large quantities of drug.

3. Synthetic Approaches to Oseltamivir

3.1. Introduction

Oseltamivir (**6**, Tamiflu, GS 4104-02, RO0640796) was discovered at Gilead Sciences and patented in 1995. In 1996, a contract with F. Hoffmann-La Roche Ltd. was signed for the codevelopment of the drug and, after only two and a half years, a New Drug Application was filed in the United States. The drug was commercially launched in November of 1999 as the phosphoric acid salt.[36] The discovery of oseltamivir came as the result of a search for a less polar molecule than DANA (**4**) or zanamivir (**5**) to prepare an orally active drug. This was accomplished by replacing the

highly polar glycerol side chain by a less polar group such as 3-pentanol. In addition, it was found that the position of the double bond was critical for the potency of the drug.[39] The highly water-soluble phosphate salt, with a serum half-life of about 3 h, is an ethyl ester prodrug that is hydrolyzed in the liver by hepatic esterases to the active form oseltamivir carboxylate **56**.[37] The drug is administered orally at a dose of 75 mg twice a day. The evaluation of oseltamivir in the treatment of influenza[13c] as well as the synthetic approaches have been previously reviewed in a number of publications.[11b,e,f,37,38]

3.2. First Synthesis of Oseltamivir Carboxylate by Gilead Sciences Inc

Acid **56** was the first molecule identified by Gilead scientists for development,[39] but the ethyl ester prodrug oseltamivir phosphate was ultimately chosen as the clinical candidate based on its potent *in vitro* and *in vivo* activities and its good oral bioavailability. The synthesis of acid **56** from (−)-shikimic acid (**42**) is depicted in Scheme 7. Epoxide **43** was prepared as described in the literature.[40] The hydroxy group was protected as the corresponding methoxymethyl ether, which, upon treatment with sodium azide in the presence of NH₄Cl, afforded azido alcohol **45**. The ring-opening was both regio- and stereospecific, and this was attributed to the esteric and electronegative inductive effect of the MOM group. Aziridine **47** was obtained by first mesylating **45** followed by azide reduction with triphenylphosphine. The aziridine ring was opened by treating with azide to give azido amine **48**. The MOM-protecting group was removed under acidic conditions to give alcohol

Scheme 8. Synthesis of Epoxide 43 from (−)-Quinic Acid (57) by Gilead Sciences Inc.
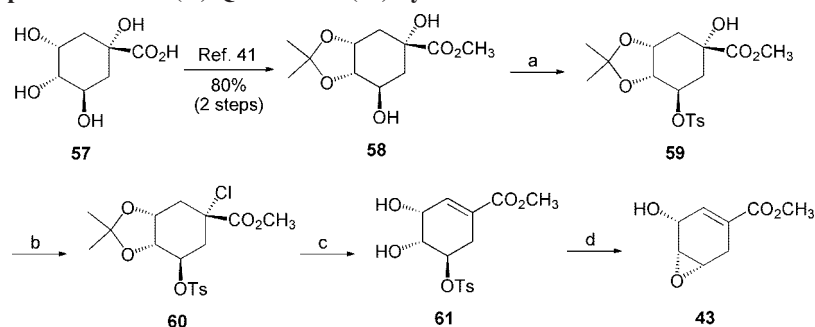
Reagents and conditions: (a) TsCl, DMAP, py, rt, 72 h, 92%. (b) SO$_2$Cl$_2$, py, -78 °C. (c) p-TsOH, MeOH, reflux, 4 h, 54% (2 steps). (d) DBU, THF, 0 °C to rt, 12 h, 100%.

49. The amino group in **49** was protected with trityl chloride followed by mesylation of the hydroxy group to give intermediate **51**, which, *in situ*, cyclized to produce protected aziridine **52**. The treatment of **52** with 3-pentanol in the presence of BF$_3$·OEt$_2$ opened up the aziridine ring to give amine **53**. The synthesis of acid **56** was completed by acetylating the amino group, reducing the azido group as before with Ph$_3$P, and hydrolyzing the methyl ester functionality under basic conditions.

The choice of (−)-shikimic acid as the starting material in this process seemed an obvious one due to the fact that the carbocyclic system is already present. This first synthesis of a close relative of oseltamivir displays some of the features found in subsequent routes, such as the introduction of the amino group at carbon 5 *via* aziridine ring-opening and the use of Lewis acid-catalyzed chemistry for placing the 3-pentyl ether functionality at carbon 3. The overall yield for this 14-step route is a remarkable 15%, despite the fact that several protecting groups were employed, and it was demonstrated on a milligram scale.

3.3. Optimized Synthesis of Epoxide Intermediate 43 by Gilead Sciences Inc

Due to the high cost and low availability of (−)-shikimic acid in large quantities, an alternative synthesis of epoxide **43** was described in the same publication that started from more readily available (−)-quinic acid (**57**, Scheme 8).

Thus, (−)-quinic acid (**57**) was converted to acetonide **58** as has been previously reported,[41] followed by tosylation of the secondary alcohol to provide tosylate **59**. The subsequent selective dehydration step proved to be challenging. In spite of the fact that a similar approach had been reported in the literature,[42] its implementation was not reproducible on scale. The researchers opted for converting the tertiary alcohol group to a chloride with sulfuryl chloride and pyridine. The concurrent acetonide hydrolysis and chloride elimination were carried out in methanol at reflux in the presence of a catalytic amount of p-toluenesulfonic acid to give diol **61**. During this step, the other olefinic regioisomer was easily aromatized under the reaction conditions and removed by recrystallization. The authors did not mention or provide any reference to explain why only the undesired regioisomer aromatized. Finally, epoxide **43** was generated by treating **61** with DBU. The synthesis of epoxide **43** from (−)-quinic acid was accomplished without resorting to chromatography for intermediate purification, and this protocol was implemented on a several hundred gram scale. Even though this route to **43** is longer and lower-yielding than the previous one from (−)-shikimic acid, the use of inexpensive and readily available (−)-quinic acid as well as the avoidance of the Mitsunobu chemistry reported to generate the epoxide functionality,[40] makes it attractive from a practical point of view.

In this same article, the researchers mentioned that ethyl ester **6** (GS4104) exhibited good oral bioavailability in several animals and was orally efficacious against influenza in the mouse and ferret models. For this reason, **6** was selected as a prodrug clinical candidate for the treatment and prophylaxis of influenza.

3.4. First Scalable Synthesis of Oseltamivir Phosphate from (−)-Quinic Acid by Gilead Sciences Inc

Once the best candidate had been identified, the need for an efficient methodology to prepare multikilogram quantities of drug was addressed at Gilead. As a result, a new synthesis of oseltamivir was designed that started, as before, from (−)-quinic acid (**57**, Scheme 9).[43] Thus, **57** was first converted to acetonide **62** by a modified literature procedure,[39,41] and this intermediate was then treated with a catalytic amount of sodium ethoxide in ethanol to obtain a **62:64** mixture in a 1:5 ratio. Since the separation of this mixture by fractional crystallization was inefficient on scale, the crude was treated with methanesulfonyl chloride to provide a mixture of mesylates **63** and **65** in the same 1:5 ratio. The undesired and highly crystalline mesylate **63** was removed by filtration, and from the filtrates, mesylate **65** was isolated. The dehydration of **65** was carried out with sulfuryl chloride[44] to provide a mixture of alkenes **66** and **67** in a 4:1 ratio. As a side product, oily chloride **68** was also obtained in 10−15% yield. Attempts to obtain pure **66** from the reaction mixture by means of high-throughput fractional crystallization failed due to the high crystallinity of both alkenes. Instead, the three-component mixture was treated with pyrrolidine and (Ph$_3$P)$_4$Pd as catalyst,[45] which resulted in the conversion of mesylate **67** to pyrrolidino derivative **69**. Intermediate **69** was then removed from the reaction mixture by aqueous sulfuric acid extraction, and the desired mesylate **66** was isolated after recrystallization from ethyl acetate/hexane. The synthesis continued with the transketalization of acetonide **66** with 3-pentanone and perchloric acid as catalyst to generate ketal **70**.[46] The authors mentioned that a more concise route that employed the 3,4-pentilidene ketal analogues of **62**, **63**, **64**, and **65** was not implemented on scale due to the lack of crystallinity of these compounds. Ketal **70** was opened by treatment with trimethylsilyl trifluoro-

Scheme 9. First Large Scale Synthesis of Oseltamivir Phosphate by Gilead Sciences Inc.
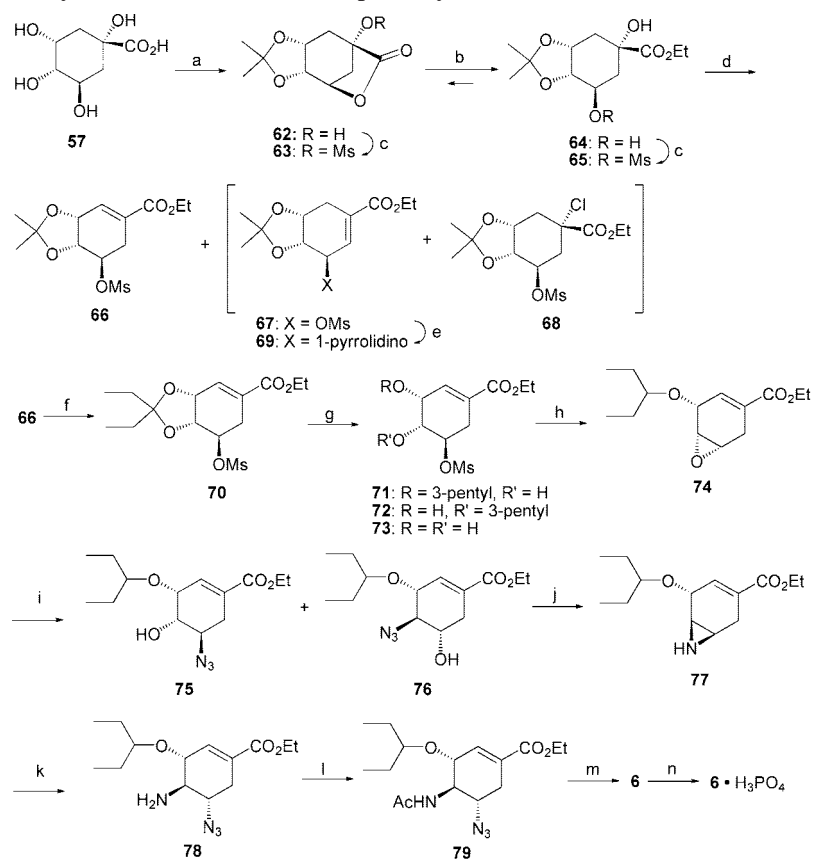
Reagents and conditions: (a) 2,2-dimethoxypropane, *p*-TsOH, acetone, reflux, 2 h; (b) NaEtO, EtOH (abs), rt, 2 h, **62**:**64** ratio: 1/5; (c) MsCl, TEA, CH$_2$Cl$_2$, 0-5 °C, 1.5 h; yield of **65**: 69% (three steps); (d) SO$_2$Cl$_2$, py, CH$_2$Cl$_2$, -20 to -30 °C; **66**:**67**:**68** ratio: 4:1:1; (e) **66**:**67**:**68** mixture, pyrrolidine, (Ph$_3$P)$_4$Pd, EtOAc, 35 °C, 3.5 h; yield of **66**: 30% from **57**; (f) 3-pentanone, HClO$_4$, 40 °C, 25 mmHg, 95%; (g) TMSOTf, BH$_3$·Me$_2$S, CH$_2$Cl$_2$, -10 to -20 °C, 45 min, **71**:**72**:**73** ratio: 10:1:1, 75%; (h) KHCO$_3$, EtOH/H$_2$O, 55-65 °C, 1 h, 96%; (i) NaN$_3$, NH$_4$Cl, EtOH/H$_2$O, 70-75 °C, 12-18 h; **75**:**76** ratio: 10:1, 85%; (j) Me$_3$P, MeCN, <38 °C, 2 h, 97%; (k) NaN$_3$, NH$_4$Cl, DMF, 70-80 °C, 12-18 h; (l) Ac$_2$O, NaHCO$_3$, hexanes/CH$_2$Cl$_2$, 1 h, 44% (2 steps); (m) H$_2$ (1 atm), Ra-Ni, EtOH, 10-16 h; (n) H$_3$PO$_4$, EtOH, 55-65 °C to 0 °C, 3-24 h, 71% (2 steps).

methanesulfonate and BH$_3$·Me$_2$S complex[47] to provide a mixture of ethers **71** and **72** and diol **73** in a 10:1:1 ratio. The best regioselectivity was obtained by adding small portions of aqueous sodium bicarbonate to the freshly prepared reaction mixture at −20 °C. Since the separation of **71**, **72**, and **73** was not possible through fractional crystallization or distillation, the crude three-component mixture was heated in aqueous ethanol in the presence of potassium bicarbonate to provide epoxide **74**, which could be selectively extracted into hexanes. The introduction of the amino functionality at the carbon 5 position on the ring was accomplished through azide chemistry. Thus, the reaction between epoxide **74** and sodium azide in aqueous ethanol provided a 10:1 mixture of alcohols **75** and **76**, respectively. The crude was reduced and cyclized in the presence of trimethylphosphine[48] to give aziridine **77**. Triphenylphosphine with a catalytic amount of triethylamine hydrochloride could also be used for this transformation, but this protocol required a more complex workup to remove the triphenylphosphine oxide generated during the reaction. Sodium azide was also used for the opening of aziridine **77** to provide azide **78**, which was acylated under Schotten–Baumann conditions with acetic anhydride to give intermediate **79**. This material was highly crystalline and was chosen as the final intermediate toward the synthesis of the API. The preparation of oseltamivir phosphate was completed by first reducing the azide functionality with hydrogen (1 atm) and Raney

nickel.[49] As an alternative to the azide Raney nickel reduction, trimethylphosphine in moist THF could also be employed.[50] Finally, the addition of phosphoric acid precipitated the phosphate salt as feathery needles. The same researchers also prepared the hydrochloride salt, but it was an amorphous solid. The synthetic route from (−)-quinic acid consisted of 12 steps and 4.4% overall yield. This methodology has been implemented in standard pilot plant equipment to produce kilogram quantities of oseltamivir phosphate.

This synthetic approach represents a truly scalable process that has been demonstrated on a kilogram scale and with 4.4% overall yield. The fact that Gilead had to resort to azide chemistry in two instances to introduce the two amino groups at positions 4 and 5 on the ring makes it an even more remarkable achievement. Only three crystalline intermediates were isolated, no chromatography was required, and minimal protecting group chemistry was necessary throughout the route. In addition, some clever chemistry was developed, such as the conversion of mesylate **67** to the corresponding 1-pyrrolidino derivative to allow for the purification of mesylate **66**. Even though it is highly unlikely that this route could become an industrial process without some modifications, it represents a good compromise to prepare large quantities of drug to advance the clinical program.

Scheme 10. Optimized Route to Epoxide 74 from (−)-Quinic Acid−Synthesis of α-Hydroxy Ester 64 by F. Hoffmann-La Roche Ltd
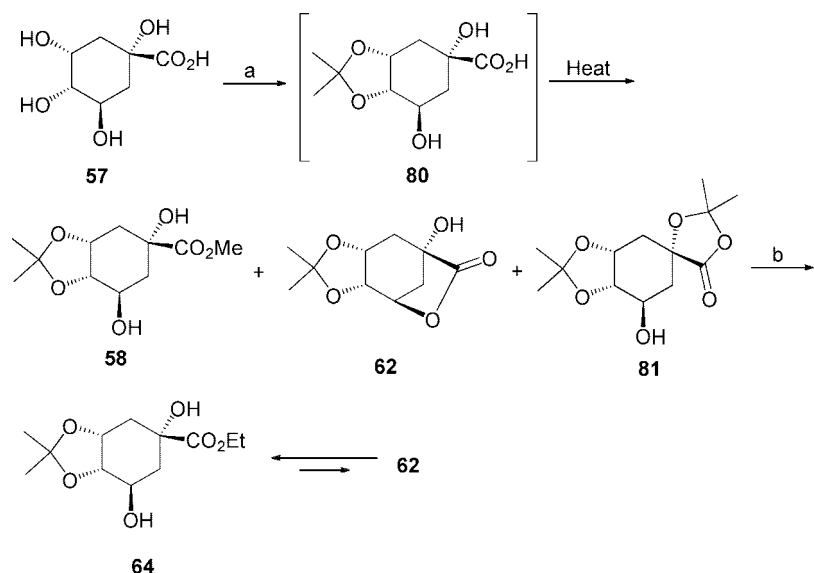
Reagents and conditions: (a) 2,2-dimethoxypropane, *p*-TsOH·H$_2$O, EtOAc, 70-78 °C, 1 h; **58:62:81** ratio: 6:90:2. (b) NaEtO, EtOH, -20 °C, overnight; **64:62** ratio: 13:1.
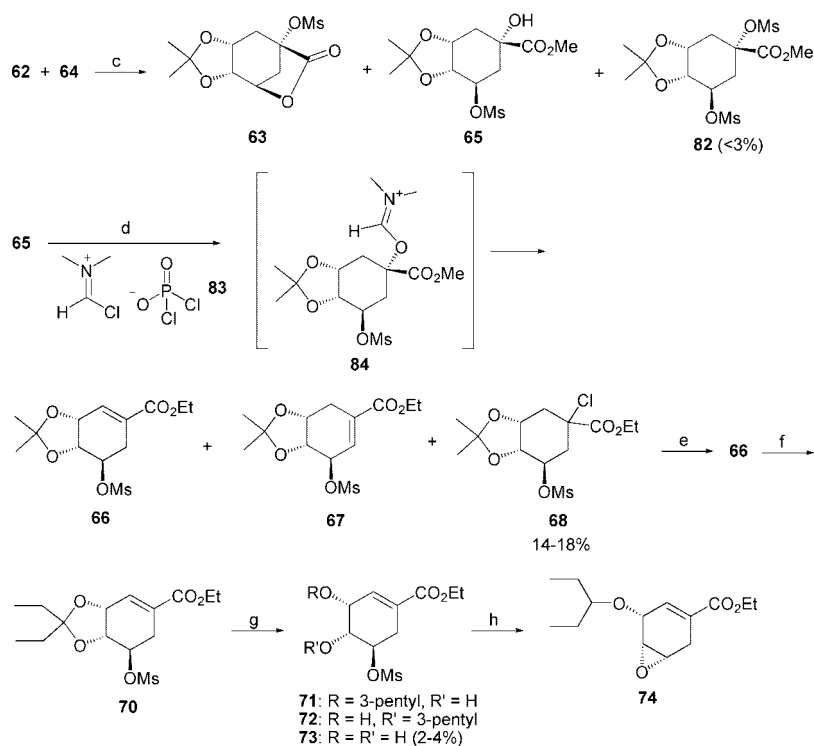
Reagents and conditions: (c) MsCl, TEA, CH$_2$Cl$_2$, 0-5 °C, 2 h. (d) **83**, EtOAc, 70-78 °C, 2 h; **66:67** ratio: 35-50:1. (e) Recrystallization from MeOH, 60-65 °C to -20 °C, 1 h, 45% from (-)-quinic acid **57**. (f) 3-Pentanone, CF$_3$SO$_3$H, 40 °C, 100-150 mbar, 98%. (g) Et$_3$SiH, TiCl$_4$, CH$_2$Cl$_2$, -32 to -36 °C, 2 h, 87%; **71:72** ratio: 32:1. (h) NaHCO$_3$, H$_2$O/EtOH, 60-65 °C, 2.5 h, 80%.

3.5. Industrial Synthesis of Epoxide 74 by F. Hoffmann-La Roche Ltd

The optimized preparation of epoxide **74**, a key intermediate en route toward the synthesis of oseltamivir, has been featured in a publication by researchers at F. Hoffmann-La Roche Ltd.[51] Two routes were developed that employ (−)-quinic acid and (−)-shikimic acid as starting materials.

The route from (−)-quinic acid (**57**) is presented in Scheme 10. The cis diol moiety in **57** was protected as the acetonide,

which was converted upon heating to a mixture of **58**, **62**, and **81**, with lactone **62** as the major product. This mixture was subjected to the reaction with sodium ethoxide in ethanol to give, at −20 °C, a 13:1 ratio of ester **64** and lactone **62**, whereas at ambient temperature the ratio was only 5:1. With the goal of stabilizing this ratio, the reaction was quenched with acetic acid at −20 °C. The **62/64** mixture was treated with a slight excess of methanesulfonyl chloride to afford the corresponding mixture of mesylates **63/65** with less than

Scheme 11. (−)-Shikimic Acid Route toward the Preparation of Ketal 70 by F. Hoffmann-La Roche Ltd
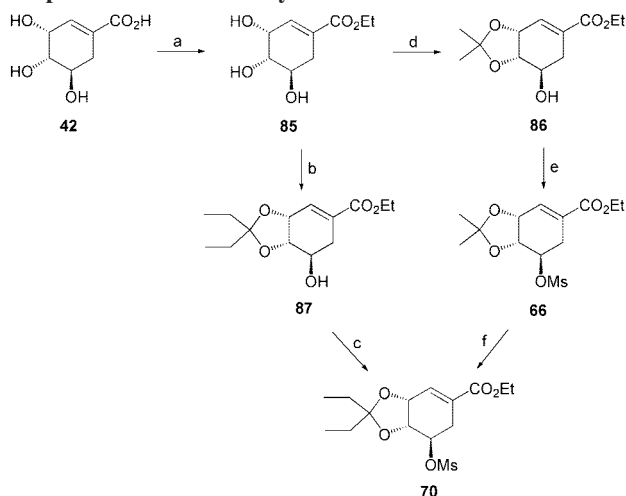
Reagents and conditions: (a) SOCl$_2$, EtOH, reflux, 3.5 h, 97%. (b) 3-Pentanone, CF$_3$SO$_3$H, 97%. (c) MsCl, TEA, CH$_2$Cl$_2$, 0-5°C, 93%. (d) Me$_2$C(OMe)$_2$, p-TsOH•H$_2$O, EtOAc, 30-35 °C, 150-200 mbar, 95%. (e) MsCl, TEA, EtOAc, 0-5 °C to 20 °C, 30 min, 82%. (f) 3-Pentanone, CF$_3$SO$_3$H, 98%.

3% of dimesylate **82** (Scheme 10 (bottom)). The purification of **65** was carried out by recrystallization from ethyl acetate, which removed most of the undesired **63**. The remaining **63** was completely removed by a hydrolytic workup in the next step. The dehydration reaction was tried under various conditions, but the best selectivity and yield were obtained with commercially available Vilsmeier's salt **83**, which can also be prepared in situ from DMF and POCl$_3$ (COCl)$_2$ or COCl$_2$.[52] The reaction proceeds through imidate ester **84**, which eliminates DMF upon heating to afford a 35−50:1 mixture of alkenes **66** and **67** and up to 18% of chloride **68**. The researchers did not provide any explanation for the selectivity of the elimination, but they highlighted the fact that chloride was necessary as base to promote the elimination, since similar processes with chloride-free Vilsmeier's salts failed to provide the desired outcome. After purifying alkene **66** by recrystallization from methanol, it was transketalized with 3-pentanone and triflic acid as catalyst to give intermediate **70**. The reductive opening of the ketal was accomplished with a combination of triethylsilane and titanium tetrachloride[53] in dichloromethane at −32 to −36 °C to generate a mixture of alcohols **71** and **72** and a small amount of diol **73**. The temperature range was found to be critical, since at lower temperatures no reaction occurred and at higher temperatures more **73** was produced. The preparation of epoxide **74** was completed by treating the crude mixture of alcohols with sodium bicarbonate in aqueous ethanol at 60 °C. Only alcohol **71** cyclized to afford **74**, whereas the unreacted **72** was removed by recrystallization.

This optimized approach to **74** doubled the yield from (−)-quinic acid, and the researchers highlighted the fact that it reduced the number of operations in the plant by 30%, a big factor in the overall cost and speed to produce any commercial material. In addition, some very interesting chemistry was implemented throughout the synthesis, such as the use of Vilsmeier's salt to dehydrate alcohol **65** and the reduction of protected diol **70** with Et$_3$SiH to give a mixture of hydroxyethers **71** and **72**.

The (−)-shikimic acid route (Scheme 11) has the advantage that the double bond is already present at the desired position in the starting material. Two different routes toward the preparation of ketal **70** were investigated. Even though

one step longer, the route that proceeds through intermediate **66** was preferred due to the fact that this material is highly crystalline and could be easily purified. In the alternative shorter route, the intermediates were oils and had to be carried through without any purification. Thus, (−)-shikimic acid (**42**) was esterified with thionyl chloride in ethanol at reflux to give ethyl ester **85**. The cis-diol functionality was protected with 2,2-dimethoxypropane and p-toluensulfonic acid as catalyst to afford ketal **86**. Mesylation of **86** under standard conditions followed by transketalization with 3-pentanone afforded ketal **70**, which can be converted to epoxide **74** as shown previously (Schemes 9 and 10).

This second alternative for the preparation of ketal **70** nicely complements the route from (−)-quinic acid and decreased the production time by 50% to access epoxide **74**. On the other hand, the limited availability of (−)-shikimic acid in large quantities and its higher cost may make this approach less attractive on scale.

3.6. Azide-Free Synthesis of Oseltamivir Phosphate by F. Hoffmann-La Roche Ltd

Another publication from the same group at F. Hoffmann-La Roche Ltd. reported an azide-free synthesis of oseltamivir phosphate from epoxide **74** (Scheme 12).[54] The goal was to find a nonazide nitrogen nucleophile that could be compatible with the rest of the functional groups on the molecule and with the strong tendency of the cyclohexene intermediates toward aromatization.

Epoxide **74** was ring-opened with allylamine and MgBr$_2$•OEt$_2$ as Lewis acid to generate intermediate **88**. Several other Lewis acid catalysts were explored (CaCl$_2$, ZnCl$_2$, MgBr$_2$•6H$_2$O, anhydrous MgBr$_2$, LiOTf, LiBr, Zn(OTf)$_2$, LiCl, BF$_3$•OEt$_2$, Sc(OTf)$_3$, and TiCl$_4$), but the result was either incomplete reactions, partial decomposition, or aromatization. After a solvent screen was carried out (MeCN, MTBE, toluene, IPA, EtOAc), it was found that a 9:1 mixture of MTBE/MeCN was optimal for this transformation. As a byproduct, regioisomer **92** (Figure 6) was also
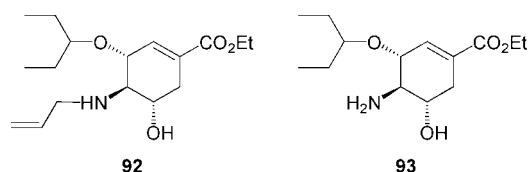
Figure 6. Byproducts from the opening of epoxide **74** and deallylation of amine **88**.

obtained (**88**:**92** ratio: 10:1 to 13:1). Benzylamine and Yb(OTf)$_3$ as catalyst[55] were also employed in the epoxide-opening step, but the conditions required for removal of the benzyl protecting group also reduced the double bond, and this approach had to be abandoned. Intermediate **88** was deallylated in the presence of 10% Pd/C[56] to give amine **89** and about 4% of the regioisomer **93** derived from **92** (Figure 6). The researchers highlighted that the addition of ethylenediamine or ethanolamine initiated and promoted the deallylation reaction.

The transformation of **89** to **90**, which introduced the second amine functionality on the molecule, was accomplished without the isolation of any of the intermediates. The detailed process is shown in Scheme 13. The amino group in **89** was protected as the benzaldehyde imine with azeotropic removal of water to give imine **94**, which was

Scheme 12. Azide-Free Synthesis of Oseltamivir Phosphate from Epoxide 74 by F. Hoffmann-La Roche Ltd
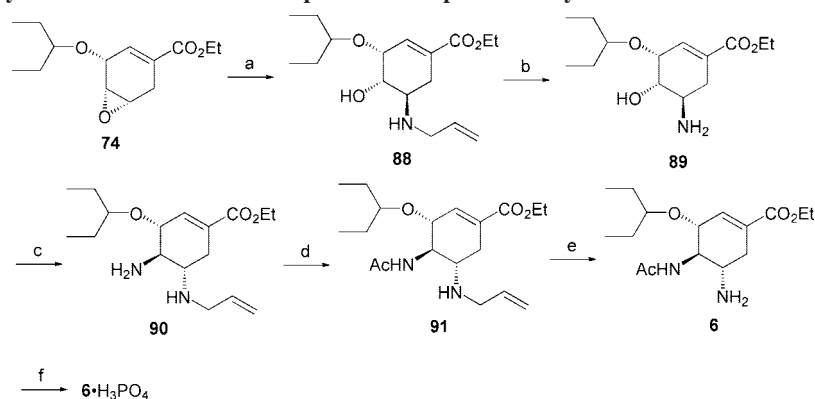
Reagents and conditions: (a) Allyl amine, MgBr$_2$•OEt$_2$, MTBE/MeCN 9:1, 55 °C, 16 h, 97%. (b) 10% Pd/C, ethanolamine, EtOH, reflux, 3 h, 77%. (c) (i) PhCHO, MTBE, reflux, 2 h; (ii) MsCl, TEA, 0-5 °C, 2.5 h; (iii) allyl amine, 110-112 °C, 15 h, 3.5-4.5 bar; (iv) HCl, H$_2$O, 80% (4 steps). (d) Ac$_2$O, AcOH, MeSO$_3$H, MTBE, 0-5 °C to rt, 14 h, 83%. (e) 10% Pd/C, ethanolamine, EtOH, reflux, 3 h. (f) H$_3$PO$_4$, EtOH, 50 °C to -25 °C, 70%.

Scheme 13. Stepwise Transformation of 89 to 90
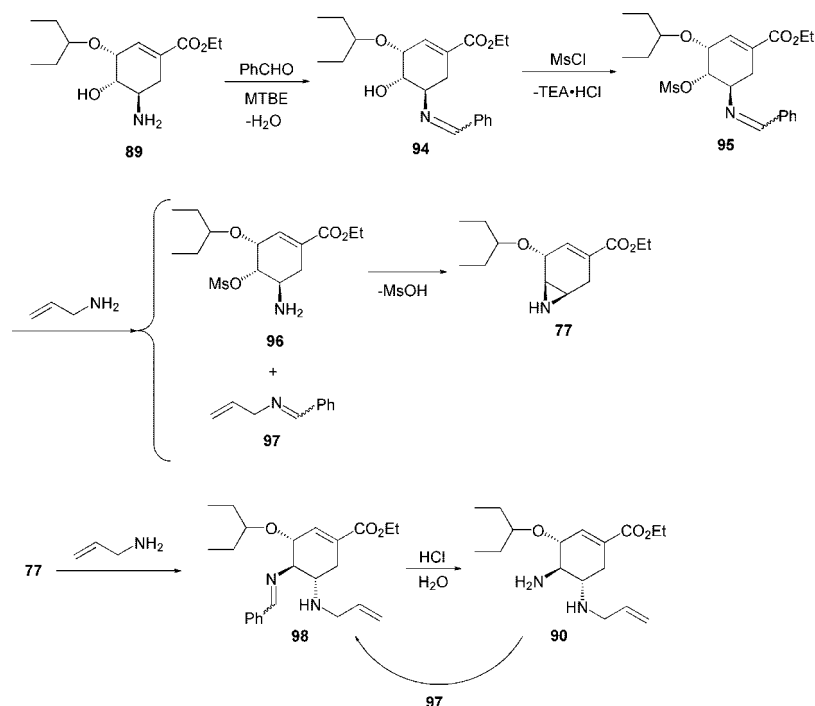
mesylated to afford intermediate **95**. After filtration of the triethylammonium chloride generated in the mesylation step, **95** was treated with allylamine in an autoclave at 112 °C to give, after acid hydrolysis, diamine **90**. The mechanism proposed in Scheme 13 is based on the production of imine **98** and the detection of both aziridine **77** and imine **97**. It was then speculated that the first step is the trans imination of **95** with allyl amine to give **96** and **97**.[57] Amine **96** immediately ring-closes to give aziridine **77**, which, in contact with the methanesulfonic acid, liberated after the aziridine formation step, forms diamine **90**. Finally, **90** undergoes another trans imination reaction with **97** to give imine **98**.

The synthesis continued with the acetylation of **90** with acetic anhydride under acidic conditions to give acetamide **91**. When this reaction was attempted under basic conditions, the allylamino nitrogen was also acetylated and there was about 20% of unreacted amine **90**. The deallylation step to generate oseltamivir also had to be carefully designed to

prevent acetyl migration,[58] which was found to be favored under acidic conditions. This transformation was successfully carried out with 10% Pd/C in ethanol in the presence of ethanolamine. The addition of an ethanolic solution of phosphoric acid completed the synthesis of oseltamivir phosphate.

The overall yield for this azide-free methodology was 35−38%, in contrast with the 27−29% yield for the azide route, and has been implemented on a multigram scale. In addition to the increase in yield and the purification of intermediates without resorting to chromatography, this approach represents the first example that avoids the traditional route to introduce nitrogen functionality on the ring, both for zanamivir and oseltamivir, using azide in any of its variations as nucleophile. A key step is the opening of epoxide **74** with allylamine to give the desired aminoalcohol **88** with very good regioselectivity.

Scheme 14. Second-Generation Route to Oseltamivir Phosphate by the Roche Colorado Corporation
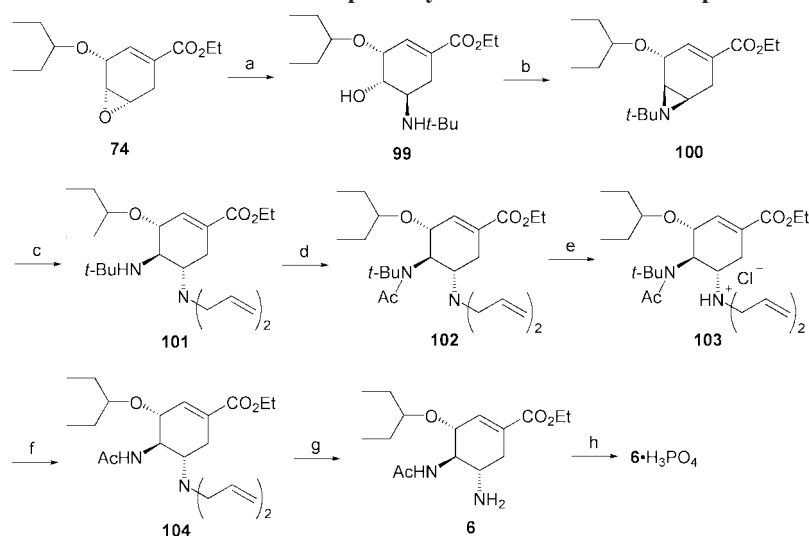
Reagents and conditions: (a) (i) *tert*-BuNH$_2$, MgCl$_2$, PhMe, 25 °C, 6 h; (ii) **74**, 50 °C, 8 h, 96%. (b) MsCl, TEA, PhMe, 5 °C to 70 °C, 3 h, 93%. (c) Diallylamine, PhSO$_3$H, 120 °C, 5.5 h, 93%. (d) Ac$_2$O, NaOAc, 110-116 °C, 4 h, 94%. (e) HCl, EtOH (abs)/heptane, 13-20 °C to -15 °C, 92%. (f) TFA, 50 °C, 1.5 h, 96%. (g) 1,3-Dimethylbarbituric acid, Ph$_3$P, Pd(OAc)$_2$, EtOH (abs), 35 °C, 2 h. (h) H$_3$PO$_4$, EtOH, 50 °C to -18 °C, 88% (2 steps).

3.7. Second Generation Route to Oseltamivir Phosphate by the Roche Colorado Corporation

A second-generation process for the synthesis of oseltamivir phosphate has been developed by researchers at the Roche Colorado Corporation (Scheme 14).[59] This synthesis also starts from epoxide **74**, but it differs from previous syntheses in that the ammonia equivalents for the opening of the epoxide and the aziridine intermediates are *tert*-butylamine and diallylamine respectively.

The reaction between epoxide **74** and a preformed *tert*-butylamine−magnesium chloride complex gave alcohol **99**. The rate of reaction to produce **99** was faster when the order of reagent addition was magnesium chloride, amine, and, finally, **74**. Mesylation of **99** and subsequent cyclization produced aziridine **100**, which was ring-opened with diallylamine and benzenesulfonic acid as catalyst to provide diamine **101**. Similar results were obtained with Lewis acids such as CuCl$_2$, CuBr$_2$, Cu(OTf)$_2$, ZnCl$_2$, Zn(OTf)$_2$, or BF$_3$·OEt$_2$. The acetylation of **101** was carried out using acetic anhydride and sodium acetate as catalyst to generate acetamide **102**. The need for a catalyst was required, since heating **101** with 2 equiv of acetic anhydride at 90 °C for 1 h resulted in low conversion. Pyridine can also catalyze this type of transformation, but due to its toxicity, a more environmentally friendly catalyst such as sodium acetate was employed. The treatment of **102** with 1 equiv of hydrogen chloride in ethanol afforded salt **103**, which could be isolated and purified. The cleavage of the *tert*-butyl group in **103** was performed with warm trifluoroacetic acid or, alternatively, with hydrogen chloride in ethanol at reflux to afford intermediate **104**. The removal of the allyl protecting groups was efficiently carried out by η^3-allyl palladium-mediated transfer and with 1,3-dimethylbarbituric acid as the nucleophilic scavenger.[60] This protocol allowed for the direct transfer of the reaction mixture into the salt forming step to give oseltamivir phosphate.

The overall yield for this optimized route from epoxide **74** was 61%, compared to the lower yields obtained in the previous routes developed at Gilead (27−29%)[43] and Roche-Basel (35−38%).[54] In addition, no chromatography was required for intermediate purification, which should make this approach a serious contender toward the development of a commercial route to oseltamivir.

3.8. (−)-Shikimic Acid and (−)-Quinic Acid-Free Routes to Oseltamivir Phosphate by F. Hoffmann-La Roche Ltd

Some new approaches to oseltamivir that do not employ either (−)-shikimic acid or (−)-quinic acid as starting materials have also been reported by scientists at F. Hoffmann-La Roche Ltd.[36]

3.8.1. Diels−Alder Approach

The first of these approaches (Scheme 15)[61] started with the Diels−Alder reaction between readily available furan (**105**) and ethyl acrylate (**106**) to provide racemic **107**, favoring the desired *exo*-isomer in a 9:1 ratio. Several Zn and Mg catalysts were screened, and inexpensive ZnCl$_2$ proved to be the best Lewis acid for this transformation. The *exo-endo* ratio was dependent upon reaction times, and it was determined that the *endo* product was the kinetically preferred isomer and that, upon increasing the reaction time, the amount of the thermodynamically preferred exo product increased until the final 9:1 ratio was obtained. For the resolution of **107** *via* hydrolysis of the ester group, 83 microorganisms and 50 enzymes were screened. The enzyme Chirazyme L-2 gave preliminary moderate ee's that could be improved by optimizing the reaction conditions. Thus, it was found that low temperatures and nonpolar cosolvents gave higher enantioselectivities. On the other hand, high pH and substrate concentration had a deleterious effect. The optimal conditions involved running the reaction in a biphasic mixture of methylcyclohexane and pH 8 aqueous buffer at 1 °C and 5% concentration, which gave 97% ee at 75% conversion. One of the highlights of this process is that both enantiomers of the *endo*-isomer were unaffected by the enzyme and could be removed by distillation. The reaction of (−)-**107** with diphenylphosphoryl azide (DPPA) in toluene at 70 °C provided a 2:1 mixture of *exo*-triazoles **108** and

Scheme 15. Diels−Alder Approach for the Synthesis of Advanced Intermediate 116 by F. Hoffmann-La Roche Ltd
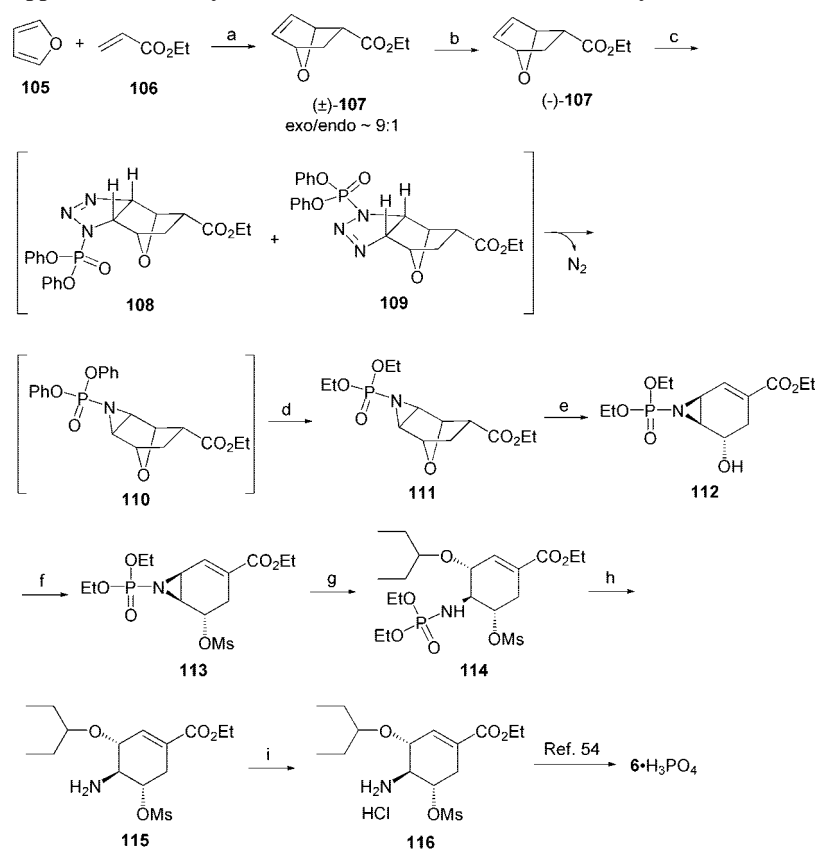
Reagents and conditions: (a) ZnCl$_2$, neat, 50°C, 72 h, 77%; (b) (i) Chirazyme L-2, methylcyclohexane, aqueous pH 8 buffer, 1 °C; (ii) distillation, 97% ee, 20% at 75% conversion. (c) DPPA, PhMe, 70 °C, 18 h. (d) NaOEt, EtOH, rt, 1 h, 53%. (e) NaHMDS, THF, -60 °C, 15 h, 94%. (f) MsCl, TEA, CH$_2$Cl$_2$, rt. (g) 3-Pentanol, BF$_3$·OEt$_2$, CH$_2$Cl$_2$, 62% (2 steps). (h) 20% H$_2$SO$_4$, EtOH, 70 °C, 22 h; (i) HCl, EtOH, 68% (2 steps).

109 *via* a [3 + 2]-cycloaddition which, after N$_2$ extrusion, provided *endo*-aziridine 110. Only *exo*-triazol 108 could be isolated after chromatography due to the instability of 109 under those conditions, and its *exo* stereochemistry was confirmed by X-ray analysis. The researchers highlighted that, at this point, they do not have a clear explanation for this unexpected inversion, but they proposed the possibility of an equilibrium in the [3 + 2]-cycloaddition that would produce a small amount of *endo*-triazol. Since this stereoisomer is more strained than the *exo*-adduct, it would extrude nitrogen faster and this would lead to the observed *endo*-aziridine. Without isolation, 110 was transesterified with NaOEt to afford diethylphosphoryl ester 111. This conversion to the diethyl analogue was necessary to avoid significant decomposition during the cleavage of the phosphorus−nitrogen bond. The *endo* stereochemistry of this intermediate was confirmed after ester hydrolysis to the corresponding acid (LiOH in THF/MeOH/H$_2$O at 60 °C) and X-ray crystallography. The synthesis continued with the ring-opening of 111 with base to afford alcohol 112, which was mesylated under standard conditions to produce intermediate 113. The aziridine ring was then opened with 3-pentanol followed by the cleavage of the diethylphosphoryl group under acidic conditions and treatment with HCl in ethanol to give salt 116. From this intermediate, the synthesis of oseltamivir can be completed as has been shown before.[54]

The main advantages of this approach are the use of very inexpensive starting materials and reagents, minimal protecting group chemistry, and the fact that the resolution of racemic material is carried out very early in the synthesis, which should considerably increase the throughput. However, the low overall yield and the use of azide are detrimental. No information was provided about the scale.

3.8.2. Desymmetrization Approach

In the same publication,[36] a second approach to oseltamivir that does not rely on either (−)-shikimic acid or (−)-quinic acid as starting material was disclosed (Scheme 16).[62] The synthesis started with the reaction between readily available and inexpensive 1,6-dimethoxyphenol (117) and mesylate 118 with potassium *tert*-butoxide as base to afford ether 119. Dibromination followed by palladium-catalyzed double ethoxycarbonylation provided diester 121. The aromatic ring was hydrogenated with Ru−Al$_2$O$_3$ (Ru-Alox) as catalyst at 100 bar to give the all-cis *meso*-diester 122, and the methyl ethers were cleaved with TMSI, generated *in situ* from TMSCl and NaI, to give diol 123. Desymmetrization of 123 with pig liver esterase (PLE)[63] produced (*S*)-(+)-mono acid 124 in excellent ee (96−98%). Increasing the reaction temperature to 35 °C considerably accelerated this transformation without sacrificing enantioselectivity (96% ee), and the enzyme tolerated up to a 10% concentration of substrate. The synthesis continued with the Shioiri−Yamada−Curtius reaction of 124 in the presence of diphenyl phosphoryl azide, which introduced the 5-amino functionality to afford oxazolidinone 125. Boc-protection followed by treatment with a catalytic amount of NaH resulted in the selective formation

Scheme 16. Diester 123 Desymmetrization toward the Synthesis of Oseltamivir by F. Hoffmann-La Roche Ltd
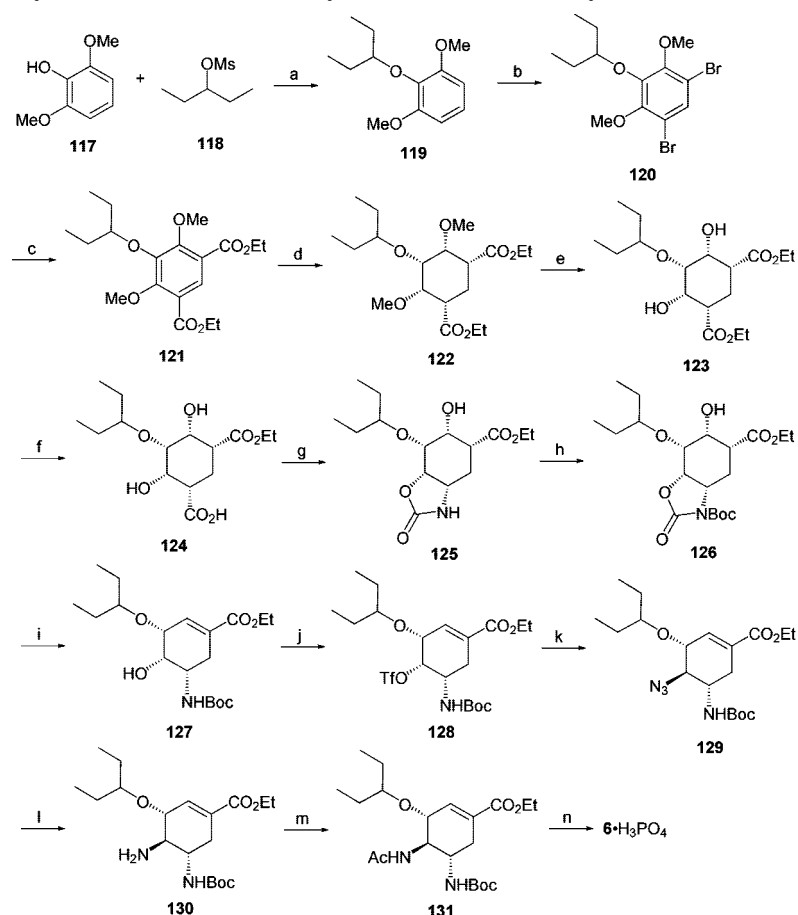
Reagents and conditions: (a) KOt-Bu, DMSO, 50 °C. (b) NBS, DMF, 0 °C, 90% (2 steps). (c) CO (10 bar), Pd(OAc)$_2$ (0.5%), 1,3-bis(diphenylphosphino)propane, KOAc, EtOH, 110 °C, 20 h, 95%. (d) H$_2$ (100 bar), Ru-Alox (5%), EtOAc, 60 °C, 24 h, 82%. (e) TMSCl, NaI, MeCN, 40 °C, 97%. (f) PLE, H$_2$O, 35 °C, pH 8.0, 96%, 96-98% ee. (g) DPPA, TEA, CH$_2$Cl$_2$, 40 °C, 81%. (h) (Boc)$_2$O, DMAP (cat.), rt. (i) NaH (cat), PhMe, reflux. (j) Tf$_2$O, py, CH$_2$Cl$_2$, -10 °C, 83% (3 steps). (k) NaN$_3$, acetone/H$_2$O, rt, 78%. (l) H$_2$, Ra-Co (or Bu$_3$P/H$_2$O). (m) Ac$_2$O, TEA. (n) (i) HBr, AcOH; (ii) H$_3$PO$_4$, EtOH, 83% (4 steps).

of the 1,2-double bond and the simultaneous cleavage of the oxazolidinone to provide alcohol **127** *via* deprotonation of the hydroxyl group followed by intramolecular attack on the oxazolidinone and CO$_2$ elimination. The proposed mechanism for this transformation is shown in detail in Scheme 17. Intermediate **127** was then treated with triflic anhydride,

Scheme 17. Proposed Mechanism for the Decarboxylative Fragmentation of Oxazolidinone 125 to Cyclohexenol 127
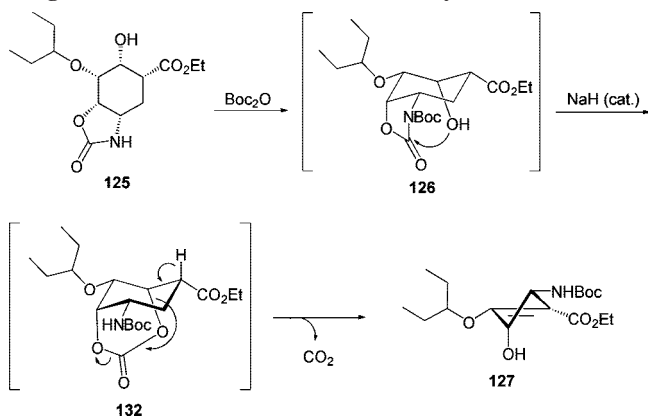
and the resulting triflate group was displaced with sodium azide to yield azide **129**. The azido group was hydrogenated with Raney-cobalt (Ra-Co) as catalyst, and the resulting

amine was treated with acetic anhydride to generate acetamide **131**. The removal of the Boc-protecting group under acidic conditions followed by the reaction with phosphoric acid completed the synthesis of oseltamivir phosphate.

Unlike the previous approach, this route is high-yielding (28%) even though it requires a larger number of transformations. It also starts from readily available and inexpensive starting materials. On the other hand, the desymmetrization step is carried out after five transformations, which would affect the throughput, more protecting group manipulation is needed, and it employs azide and DPPA as nitrogen nucleophiles. As for the Diels−Alder approach, no information on scale was provided.

3.9. Synthesis of Oseltamivir Phosphate *via* an Asymmetric Diels−Alder Reaction by Corey's Group

Corey's group at Harvard has reported an enantioselective synthesis of oseltamivir phosphate[64] (Scheme 18) that starts with the Diels−Alder reaction between 1,3-butadiene (**133**) and 2,2,2-trifluoroethyl acrylate (**134**) in the presence of catalyst **135**. This transformation has been previously reported,[65] and it can be run on multigram scale at ambient temperature to provide adduct **136** in excellent yield and enantioselectivity. In addition, the chiral ligand can be easily recovered. The trifluoroethyl ester was subjected to am-

Scheme 18. Corey's Synthesis of Oseltamivir Phosphate
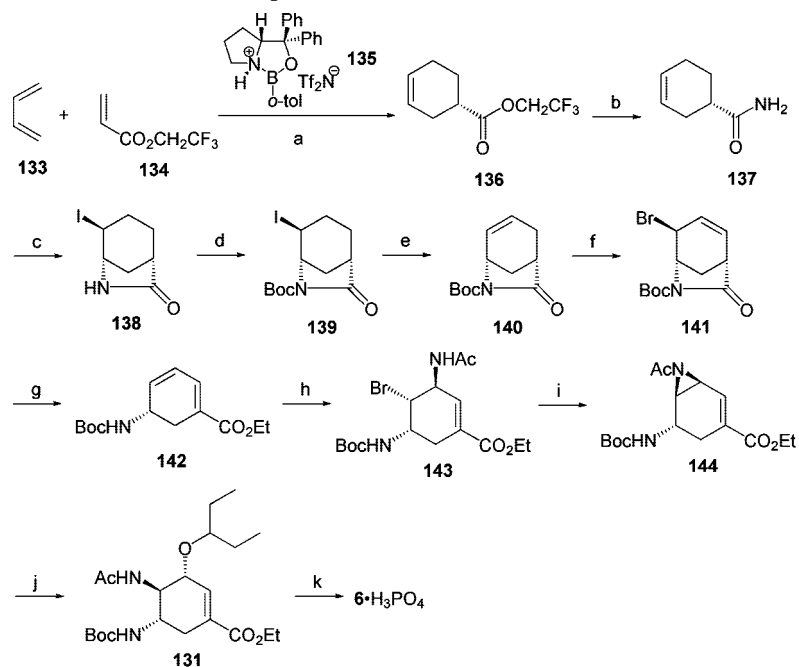
Reagents and conditions: (a) **135** (10 mol%), neat, 23 °C, 30 h, 97%, >97% ee. (b) NH$_3$, CF$_3$CH$_2$OH, 40 °C, 5 h, 100%. (c) (i) TMSOTf, TEA, pentane; (ii) I$_2$, Et$_2$O/THF, 2 h, 84%. (d) (Boc)$_2$O, TEA, DMAP, CH$_2$Cl$_2$, 4 h, 99%. (e) DBU, THF, reflux, 12 h, 96%. (f) NBS, AIBN (cat.), CCl$_4$, reflux, 2 h, 95%. (g) Cs$_2$CO$_3$, EtOH, 25 min, 100%. (h) SnBr$_2$ (5 mol%), N-bromoacetamide, MeCN, -40 °C, 4 h, 75%. (i) n-Bu$_4$NBr, KHMDS, DME, -20 °C, 10 min, 82%. (j) Cu(OTf)$_2$ (cat.), 3-pentanol, 0 °C, 12 h, 61%. (k) H$_3$PO$_4$, EtOH.

monolysis to give amide **137**, which underwent iodolactonization[66] followed by protection in the presence of di-*tert*-butyl dicarbonate to afford iodide **139**. This intermediate was dehydroiodinated with DBU, and the resulting alkene **140** was brominated at the allylic position with NBS to produce bromide **141**, whose structure was confirmed by single-crystal X-ray diffraction analysis. HBr elimination with cesium carbonate in ethanol gave diene **142**, and this substrate then underwent a novel SnBr$_4$-catalyzed bromoacetamidation reaction at low temperature, leading to intermediate **143**. This transformation was completely regio- and stereoselective, and the stereochemistry of the racemic methyl ester equivalent was determined by single-crystal X-ray diffraction analysis. The authors rationalized the outcome through the transfer of a Br$^+$ ion from a SnBr$_4$-N-bromoacetamide complex to the γ,δ-double bond of the diene followed by nucleophilic attack on the intermediate bromonium ion. The reaction of **143** with a combination of tetra-*n*-butylammonium bromide and KHMDS to generate tetra-*n*-butylammonium hexamethyldisilazane *in situ* gave acylaziridine **144**. The aziridine ring was opened up with 3-pentanol in the presence of a catalytic amount of Cu^{2+} to provide ether **131**. The removal of the Boc-protecting group and subsequent phosphoric salt formation completed the synthesis of oseltamivir phosphate.

The overall yield for this 11-step route is 27% and it has been implemented on a milligram scale, but according to the authors, some of the steps are still undergoing optimization to make this technology amenable for scale-up. Some of the highlights are the very high yield and ee of the scalable asymmetric Diels–Alder reaction, the excellent regio- and stereoselectivity of the bromoacetamidation step to generate **141**, and the unusual approach to introduce the amino functionalities on the ring. However, before this route can

be considered amenable for scale-up, several points would have to be addressed, such as the replacement of CCl$_4$ by a more environmentally friendly solvent and the cost of goods.

3.10. Synthesis of Corey's Intermediate 142 by Okamura's Group

Recently, the group of Okamura at Kagoshima University in Japan has published a short synthesis of racemic Corey's intermediate **142** (*vide supra*) as shown in Scheme 19.[67] The synthesis started with the base-catalyzed Diels–Alder reaction between N-nosyl-3-hydroxy-2-pyridone (**145**)[68] and ethyl acrylate (**146**) in water to give bicyclolactam adduct **147**. This transformation could be scaled up to produce multigram quantities of the adduct in comparable yield. The lactam carbonyl was chemoselectively reduced with NaBH$_4$ to give diol **148**. The nosyl protecting group was cleaved with a mixture of thiophenol and K$_2$CO$_3$[69] to afford amine **149**, which, without isolation, was reprotected as the Boc-derivative **150** in aqueous solution.[70] The 1,2-diol moiety was cleaved with NaIO$_4$ to produce a mixture of tautomers **151** and **152**. Reduction of the carbonyl group followed by mesylation of the resulting alcohol and elimination gave the target racemic ester **142**. The asymmetric synthesis of **142** is currently being evaluated by this same group.[71]

Even though this route to racemic **142** represents an alternative to Corey's, the preparation of starting material **145** requires additional steps and the overall yield is much lower (11% vs 73% of Corey's route). Furthermore, the racemic product would have to be eventually resolved to provide optically pure oseltamivir, with the concomitant loss of at least 50% of material.

Scheme 19. Synthesis of Racemic Corey's Intermediate 142 by Okamura's Group

Ns = 2-nitrobenzenesulfonyl

Reagents and conditions: (a) NaOH, H_2O, rt, 24 h, 83%. (b) $NaBH_4$, THF, 0 °C, 2 h, 77%. (c) PhSH, K_2CO_3, MeCN, rt, 3 h. (d) $(Boc)_2O$, H_2O, rt, 24 h, 55% (2 steps). (e) $NaIO_4$, H_2O/THF, 0 °C, 3 h. (f) $NaBH_4$, EtOH. (g) MsCl, TEA, DMAP, CH_2Cl_2, 33% (3 steps).
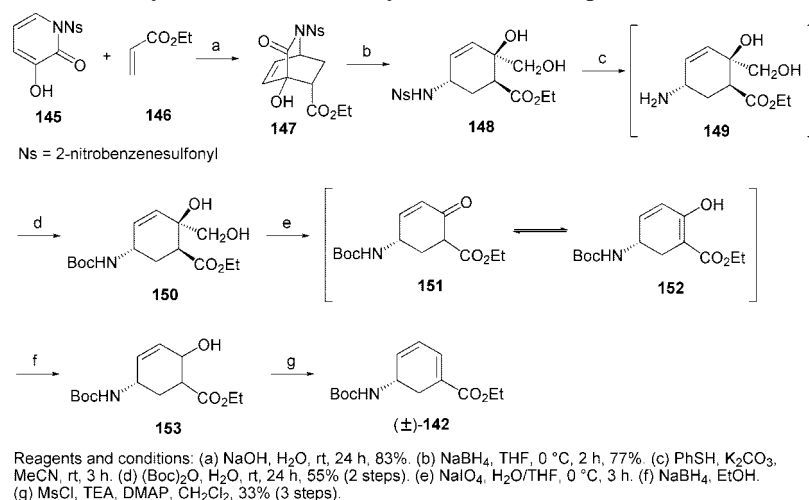
3.11. Synthetic Approaches to Oseltamivir Phosphate by Shibasaki's Group

The Shibasaki group at the University of Tokyo has recently published four different approaches toward the preparation of oseltamivir phosphate. The first approach is a *de novo* synthesis based on the asymmetric ring-opening of *meso*-aziridines with $TMSN_3$.[72] The second communication also relies on this same approach but considerably improves it.[73] The third generation route features a Diels−Alder reaction and a Curtius rearrangement as the key steps.[74] The fourth generation route showcases a barium-catalyzed asymmetric Diels−Alder reaction as the means to assemble the cyclohexene ring.[75]

3.11.1. First Generation Synthesis of Oseltamivir Phosphate via a Catalytic Asymmetric Ring-Opening Reaction of meso-Aziridines with TMSN₃

This methodology employs a yttrium catalyst prepared from $Y(Oi\text{-}Pr)_3$ and ligand **154** (Figure 7).[72]
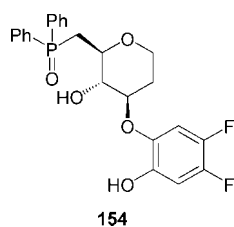
Figure 7. Structure of the ligand for the asymmetric ring-opening of *meso*-aziridines with $TMSN_3$.

The synthesis, shown in Scheme 20, started with *N*-3,5-dinitrobenzoylaziridine **155**, which was ring-opened with $TMSN_3$ in the presence of the yttrium catalyst to give azide **156**. Several rare earth alkoxides were screened with elements such as Gd, Dy, Er, Yb, and Sc, but $Y(Oi\text{-}Pr)_3$ was determined to be the best choice for this transformation. Azide **156**, whose enantiomeric purity could be enhanced through recrystallization from IPA, was treated with di-*tert*-butyl dicarbonate to afford intermediate **157**. Removal of the benzoyl group under basic conditions followed by azide reduction and protection of the resulting amine provided C_2 symmetric dicarbamate **160**. The allylic oxidation of **160** was carried out with SeO_2[76] in the presence of Dess−Martin periodinane to give a mixture of alcohol **161** and ketone **162**

in an about 2:3 ratio. The crude alcohol−ketone mixture was further treated with additional Dess−Martin periodinane to complete the oxidation to ketone **162** in fair yield. Recrystallization of **162** from IPA/hexane provided enantiomerically pure material (>99% ee), which was subjected to a 1,4-addition of TMSCN and 10 mol % of $Ni(COD)_2$ as catalyst to provide nitrile **163**. The double bond functionality was installed through oxidation with NBS and the keto group was stereoselectively reduced with bulky $LiAlH(Ot\text{-}Bu)_3$[77] to afford alcohol **165**. Aziridine **166**, prepared under Mitsunobu conditions from **165**, was ring-opened with 3-pentanol and $BF_3 \cdot OEt_2$ as Lewis acid[39] to give ether **167**. The Boc-protecting groups in **167** were removed with TFA, and the less sterically hindered amino group was reprotected to produce intermediate **169**. The synthesis of oseltamivir phosphate was completed by acetylating the free amino group, simultaneous deprotection, and conversion of the nitrile group to an ethyl ester under acidic conditions and phosphate salt formation in ethanol.

This first generation synthesis by Shibasaki also avoids the use of either (−)-shikimic or (−)-quinic acid and provides another valuable approach to oseltamivir, even though at the cost of a 17-step synthesis with very low overall yield (1.4%). The high enantioselectivity of the aziridine opening coupled with the optical upgrade after recrystallization of intermediate **162** provides a good handle to access the drug in high ee. Some drawbacks are the preparation of *meso*-aziridine **155**, which adds steps to the process, and the required protecting group manipulation. Also, alternatives to the SeO_2 and DMP oxidations and the Mitsunobu reaction to generate protected aziridine **166** would have to be found to turn it into a safer and scalable process.

3.11.2. Second Generation Synthesis of Oseltamivir via Asymmetric Ring-Opening of meso-Aziridines with TMSN₃ and Allylic Rearrangement

This more practical synthetic route still relies on the technology described in the previous scheme but avoids its two main drawbacks, namely the use of a stoichiometric amount of SeO_2 to accomplish an allylic oxidation and the protecting group shuffling at the later stages of the synthesis (Scheme 21).[73]

The synthesis started with the same sequence of reactions shown in Scheme 20 leading to amine **159**. The first step was optimized, and it only required 1 mol % of catalyst. In

Scheme 20. Shibasaki's Synthesis of Oseltamivir Phosphate *via* the Asymmetric Ring-Opening of *meso*-Aziridines with TMSN$_3$
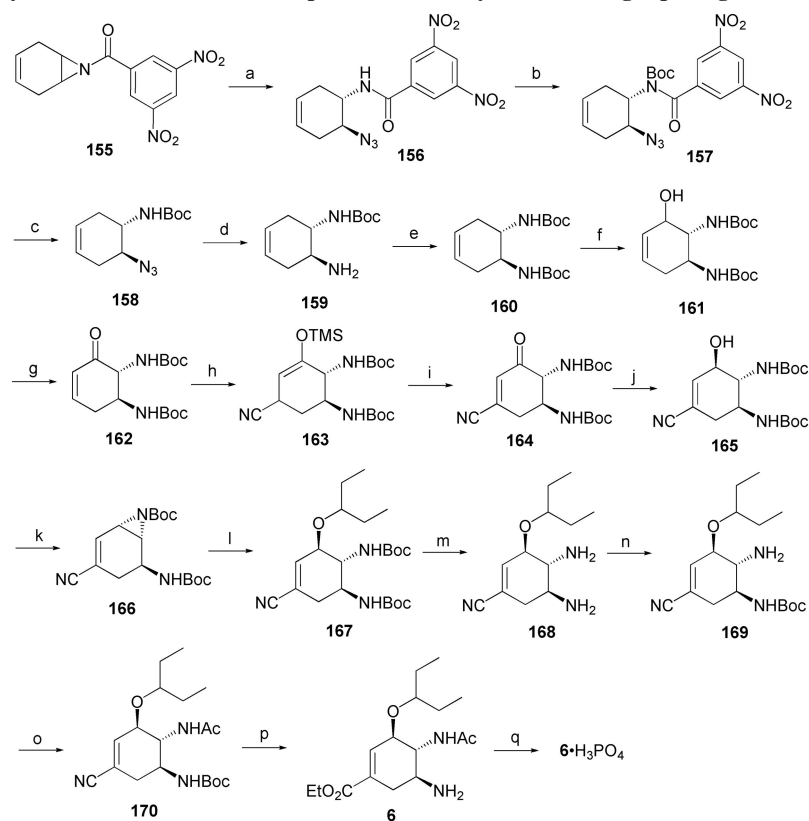
Reagents and conditions: (a) (i) Y(O*i*-Pr)$_3$ (2 mol%), **154** (4 mol%), TMSN$_3$ (1.5 eq), CH$_3$CH$_2$CN, rt, 48 h, 96%, 91% ee; (ii) recrystallization from IPA, 72%, 99% ee. (b) Boc$_2$O, DMAP, MeCN, rt, 3 h. (c) 4 M NaOH, rt, 2 h, 98% (2 steps). (d) (i) Ph$_3$P, MeCN, 50 °C, 3 h; (ii) H$_2$O, 40 °C, 2 h. (e) Boc$_2$O, TEA, CH$_2$Cl$_2$, rt, 2 h, 90% (2 steps). (f) SeO$_2$, Dess-Martin periodinane, dioxane, 80 °C, 12 h. (g) (i) Dess-Martin periodinane, CH$_2$Cl$_2$, 4 °C; (ii) recrystallization from IPA/hexane, 62% (2 steps), >99% ee. (h) Ni(COD)$_2$ (10 mol%), COD (10 mol%), TMSCN, THF, 60 °C, 65 h. (i) (i) NBS, THF, 20 min; (ii) TEA, 4 °C, 40 min. (j) LiAlH(O*t*-Bu)$_3$, THF, 4 °C, 30 min, 60% (>20:1) (3 steps). (k) DEAD, Ph$_3$P, THF, 4 °C, 1 h, 87%. (l) 3-Pentanol, BF$_3$·OEt$_2$, 4 °C, 1 h, 52%. (m) TFA, CH$_2$Cl$_2$, 4 °C to rt, 3 h. (n) Boc$_2$O, TEA, CH$_2$Cl$_2$, 4 °C, 30 min, 63% (2 steps). (o) Ac$_2$O, DMAP, py, rt, 1 h, 84%. (p) (i) 4.2 M HCl·EtOH, 60 °C, 4 h; (ii) H$_2$O, 4 °C, 3 h, 53%. (q) 85% H$_3$PO$_4$ (1 eq), EtOH, 50%.

addition, the use of 1 equiv of 2,6-dimethylphenol increased the rate of reaction,[78] and only 12 h was needed compared to the 48 h of the original conditions without affecting the enantioselectivity. A further improvement was the recovery of chiral ligand **154** in 81% after extraction with base. The yttrium catalyst prepared from recovered **154** gave essentially the same results as far as yield and enantioselectivity are concerned. From **159** on is where the route diverges. Amine **159** was acetylated and the resulting amide underwent iodocyclization and HI elimination with DBU as base to afford dihydrooxazine **172**. This intermediate was hydrolyzed in the presence of CbzCl,[79] and the resulting acetate was converted to alcohol **174** with K$_2$CO$_3$ as base. The subsequent oxidation of **174** generated ketone **175** in high overall yield. The next step involved treating **175** with diethylphosphoryl cyanide[80] with a catalytic amount of LiCN[81] to give cyanophosphate **176** with excellent diastereoselectivity, which was subjected to the key allylic rearrangement[82] in toluene at 150 °C to unexpectedly provide cyclic carbamate **177** *via* intramolecular S$_N$2′ allylic substitution. The nitrogen was reprotected and cyclic carbamate **178** was cleaved with Cs$_2$CO$_3$ to provide alcohol **180**. Oxidation of the hydroxy group and further reduction with bulky LiAlH(O*t*-Bu)$_3$[72] inverted the stereochemistry of the alcohol group and set the stage for the subsequent Mitsunobu reaction[83] to provide Boc-protected aziridine **183**. The opening of **183** with 3-pentanol and BF$_3$·OEt$_2$ as Lewis acid afforded the desired **184** and 28% of cyclic carbamate **177**. With **184** on hand, the completion of the synthesis of oseltamivir phosphate

involved the selective removal of the Boc-protecting group, acetylation of the resulting amine, removal of the Cbz-protecting group, and salt formation (Scheme 21 (bottom)).[59]

This route was lengthy and still required considerable protecting group manipulation. In the same publication, the authors addressed these issues and provided a modified route that is shown in Scheme 22. The synthesis started with azide **158**, which was converted to oxazolidinone **187** in a two-step sequence that involved cyclization in the presence of iodine and elimination of HI with DBU as base. The oxazolidinone nitrogen was protected, and the azide was reduced with thioacetic acid[84] to afford acetamide **189**. Cleavage of the acetamido functionality with Cs$_2$CO$_3$ followed by oxidation of the resulting alcohol with Dess−Martin periodinane provided ketone **191**, which underwent cyanophosphorylation as before to give intermediate **192** as the only detectable stereoisomer. The best conditions for the subsequent allylic rearrangement were found to be heating **192** in a sealed tube at 140 °C followed by quenching the reaction mixture with saturated, aqueous NH$_4$Cl to provide alcohol **194** in good yield. The structure of unstable intermediate **193** was estimated by ESI-MS without isolation. Two consecutive Mitsunobu reactions inverted the stereochemistry of the hydroxy group and generated protected aziridine **196**. As before, the reaction between **196** and 3-pentanol in the presence of BF$_3$·OEt$_2$ afforded a mixture of desired **197** and 13% of cyclic carbamate **198**. The conversion of **197** to oseltamivir phosphate was carried out

Scheme 21. Second Generation Synthesis of Oseltamivir Phosphate by Shibasaki's Group
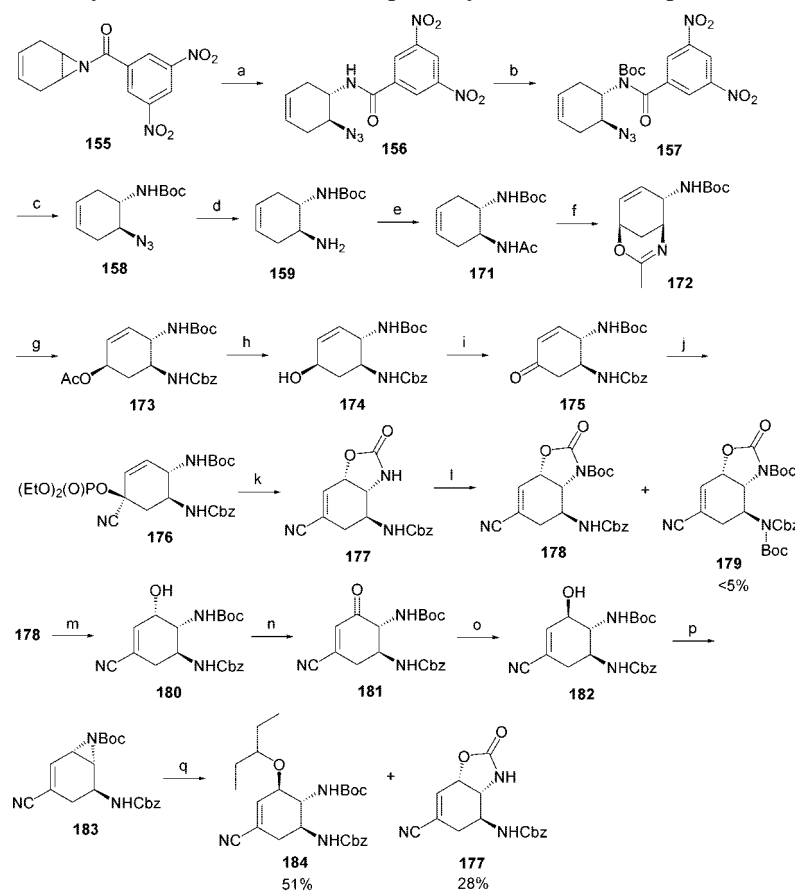
Reagents and conditions: (a) (i) Y(Oi-Pr)$_3$ (1 mol%), **154** (2 mol%), TMSN$_3$ (1.5 eq), 2,6-dimethylphenol, CH$_3$CH$_2$CN, rt, 12 h, 94%, 89% ee; (ii) recrystallization from IPA, 72%, 99% ee. (b) Boc$_2$O, DMAP, MeCN, rt, 31 h. (c) 4 M NaOH, rt, 1 h, 98% (2 steps). (d) (i) Ph$_3$P, THF, 60-70 °C, 10 h; (ii) H$_2$O, 40 °C, 21 h. (e) Ac$_2$O, py, CH$_2$Cl$_2$, rt, 2 h, 99% (2 steps). (f) (i) NIS, CH$_2$Cl$_2$/CHCl$_3$, 40-60 °C; (ii) DBU, rt, 12 h. (g) CbzCl, NaHCO$_3$, CH$_2$Cl$_2$/H$_2$O, rt, 2 h, 85% (2 steps). (h) K$_2$CO$_3$, MeOH, rt, 2 h, 99%. (i) Dess-Martin periodinane, CH$_2$Cl$_2$, rt, 16 h, 96%, 99% ee. (j) (EtO)$_2$P(O)CN, LiCN (17 mol%), THF, -20 °C, 1 h, dr = 20:1. (k) PhMe, sealed tube, 150 °C, 3 h. (l) Boc$_2$O, DMAP, py, rt, 10 h, 72% (3 steps). (m) Cs$_2$CO$_3$ (10 mol%), MeOH, rt, 3 h, 97%. (n) Dess-Martin periodinane, CH$_2$Cl$_2$, rt, 19 h, 94%. (o) LiAlH(Ot-Bu)$_3$, THF, -20 to 0 °C, 2 h, 91%. (p) DEAD, Ph$_3$P, THF, 0 °C, 3 h, 87%. (q) 3-Pentanol, BF$_3$·OEt$_2$, -20 °C, 5 h.
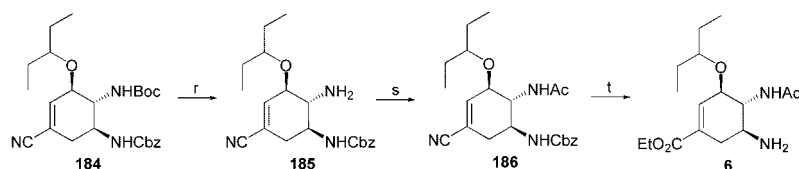
Reagents and conditions: (r) TFA, CH$_2$Cl$_2$, 0 °C to rt, 3h; (s) Ac$_2$O, TEA, CH$_2$Cl$_2$, 0 °C to rt, 16 h, 81% (2 steps); (t) (i) cc HCl, EtOH, rt, 24 h; (ii) 25% aqueous NH$_3$, rt, 10 h, 74%.

by first deprotecting with concentrated HCl in ethanol followed by the addition of H$_3$PO$_4$ as has been shown before.[59]

This optimized route has been implemented on a milligram scale, and it is more practical than the previous ones by this same group in that it is shorter and uses protecting group transformations to a lesser degree but at the expense of a lower overall yield. However, it still relies on azide chemistry to introduce the nitrogen functionality and two Mitsunobu reactions to invert the stereochemistry of the carbon 3 hydroxy group and aziridine formation. The cost of goods could also be problematic when implementing it on scale.

3.11.3. Third Generation Synthesis of Oseltamivir via Diels−Alder Reaction and Curtius Rearrangement

The third approach to oseltamivir by Shibasaki's group, unlike the two previous routes where the chirality is

introduced with the help of a chiral ligand, relies on chiral HPLC to obtain enantiomerically pure material (Scheme 23). The synthesis started with the Diels−Alder reaction between commercially available 1-(trimethylsiloxy)-1,3-butadiene (**199**) and fumaryl chloride (**200**) to give adduct **201**, which, *in situ*, was treated with TMSN$_3$[85] followed by the acidic cleavage of the trimethylsilyl ether to generate alcohol **203**. The Diels−Alder reaction gave a 2:1 *endo/exo* mixture of diastereomers, but the undesired *exo* isomer selectively decomposed during the acid treatment to cleave the silyl ether. Alcohol **203** underwent a clean Curtius rearrangement in *tert*-butanol to produce oxazolidinone **204**. The success of this transformation was attributed to the rapid intramolecular trapping of the intermediate isocyanate by the allylic alcohol and the intermolecular trapping of the second isocyanate generated by the solvent. The carbamate functionality in **204** was hydrolyzed with LiOH, and the amine

Scheme 22. Optimized Allylic Substitution Route by Shibasaki's Group
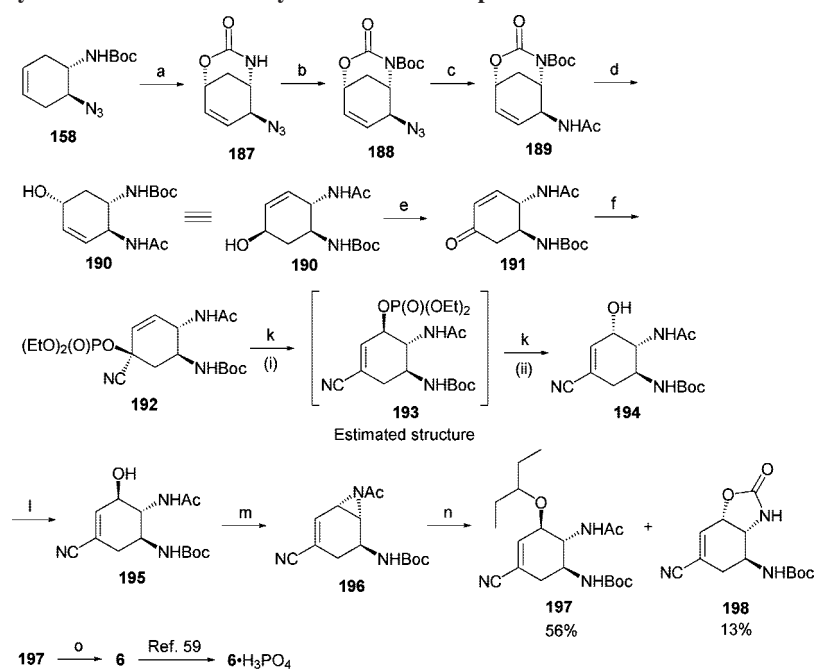
Reagents and conditions: (a) (i) I₂, K₂CO₃, KI, CHCl₃, 60 °C, 15 h; (ii) DBU, CH₂Cl₂, rt, 4 h, 85%. (b) Boc₂O, TEA, DMAP, CH₂Cl₂, rt, 2 h, 99%. (c) AcSH, 2,6-lutidine, CHCl₃, 60 °C, 19 h, 83%. (d) Cs₂CO₃ (30 mol%), n-BuOH, 4 °C to rt, 16 h, 86%. (e) DMP, CH₂Cl₂, 4 °C to rt, 15 min, 90%. (f) (EtO)₂P(O)CN, LiCN, THF, -20 °C, 4 h. (k) (i) PhMe, sealed tube, 140 °C, 40 min; (ii) satd. aq. NH₄Cl, rt, 3 h, 78% (3 steps). (l) (i) DEAD, Ph₃P, p-NO₂-C₆H₄CO₂H, THF, 4 °C, 15 min; (ii) 1 M LiOH, H₂O/THF, -20 °C, 2.5 h, 80%. (m) DEAD, Ph₃P, THF, -20 °C, 2 h, 66%. (n) 3-pentanol, BF₃·OEt₂, mol. sieves 5Å, -20 °C, 5 h, 56%. (o) cc HCl, EtOH, rt, 24 h, 60%.

Scheme 23. Third Generation Route to Oseltamivir by Shibasaki's Group
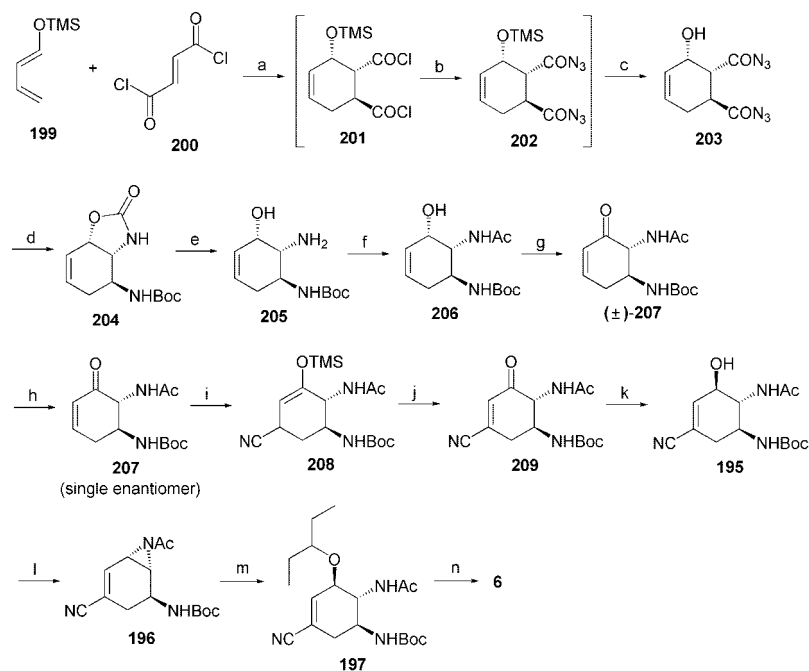
Reagents and conditions: (a) THF, rt, 2 h. (b) TMSN₃, DMAP, rt, 2 h. (c) 1 N HCl, 4°C, 10 min, 55% (3 steps). (d) t-BuOH, reflux. (e) LiOH. (f) Ac₂O, TEA. (g) Isobutyric anhydride, DMSO, 53% (4 steps). (h) Chiral HPLC. (i) TMSCN, Ni(cod)₂ (50 mol%), COD (50 mol%). (j) (i) NBS; (ii) TEA. (k) LiAlH(Ot-BuOH)₃, 44% (3 steps). (l) DEAD, Ph₃P, 66%. (m) 3-Pentanol, BF₃·OEt₂, 56%. (n) HCl, EtOH, 60%.

was acetylated to afford intermediate **206**. Oxidation of the alcohol under modified Moffat conditions[86] and chiral HPLC of the resulting ketone[87] provided enantiomerically pure ketone **207**. The Michael addition of cyanide was carried out by treating **207** with TMSCN in the presence of Ni(cod)₂ and 1,5-cyclooctadiene (COD) to give TMS-enol ether **208**. The bromination of **208** with NBS and the subsequent elimination of HBr with TEA afforded enone **209**. The

conversion of **209** to oseltamivir **6** was performed in a similar way as has been described in the previous routes.[73]

Compared to the previous routes, this third generation approach has the advantages of starting from commercially available materials and requiring minimal protecting group chemistry. It still employs azide chemistry as a means to prepare the substrate for a Curtius rearrangement that takes place in refluxing *tert*-butanol, which would most likely be

Scheme 24. Fourth Generation Synthesis of Oseltamivir by Shibasaki's Group
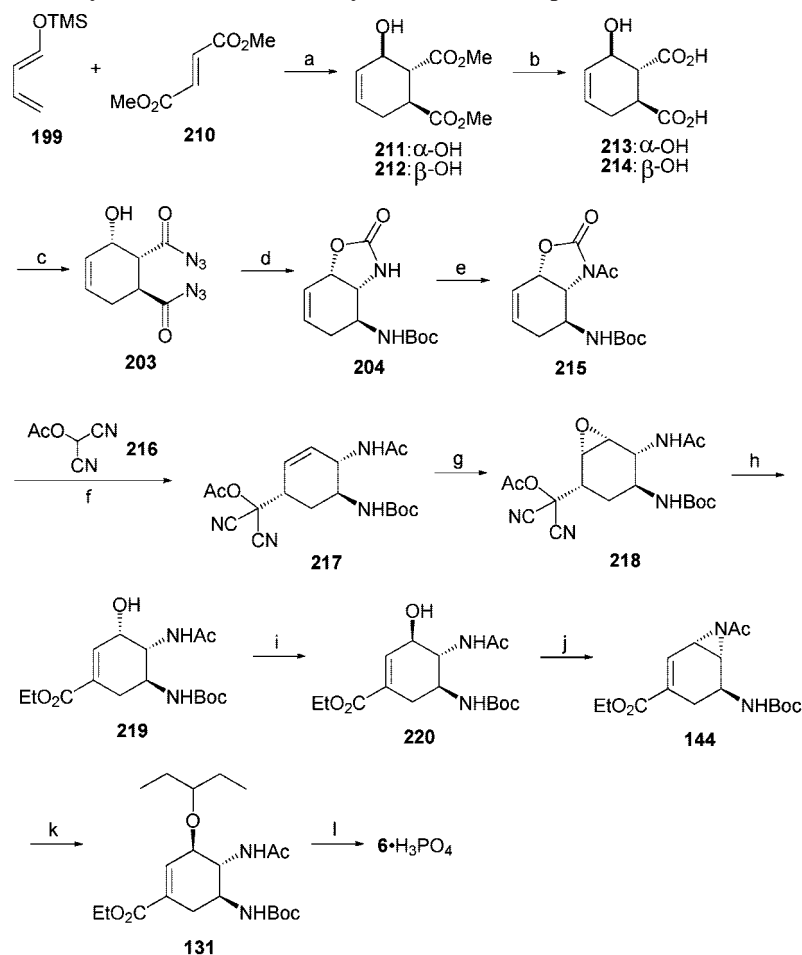
Reagents and conditions: (a) (i) Ba(Oi-Pr)$_2$ (2.5 mol%), **225** (2.5 mol%), CsF (2.5 mol%), THF, -20 °C, 36–96 h; (ii) 1 M HCl, 91%, α-OH/β-OH: 5:1, 95% ee for α-OH. (b) 2 M NaOH, MeOH, 60 °C, 10 h. (c) DPPA, TEA, THF, 0 °C, 21 h, 95% (2 steps). (d) *tert*-BuOH, 80 °C, 13 h. (e) (i) Ac$_2$O, TEA, DMAP (10 mol%), CH$_2$Cl$_2$, rt, 2.5 h; (ii) Recrystallization from CH$_2$Cl$_2$/cyclopentyl methyl ether (1:2), 80% (2 steps). (f) **216**, [Pd$_2$(dba)$_3$]·CHCl$_3$ (2 mol%), dppf (4 mol%), PhMe, 60 °C, 30 min, 85%. (g) Trifluoroperacetic acid, urea/H$_2$O$_2$, Na$_2$HPO$_4$, CH$_2$Cl$_2$, 4 °C, 2 h. (h) K$_2$CO$_3$, EtOH, rt, 5 h. (i) (i) DEAD, PPh$_3$, *p*-nitrobenzoic acid, THF, -20 °C, 1.5 h; (ii) LiOH, EtOH, 20 °C, 15 min, 65% (3 steps). (j) DIAD, Me$_2$PPh, TEA, CH$_2$Cl$_2$, 4 °C, 10 min, 76%. (k) 3-Pentanol, BF$_3$·OEt$_2$, -20 °C, 15 min, 75%. (l) (i) TFA; (ii) H$_3$PO$_4$, 73%.

ruled out on scale for safety reasons, and a Mitsunobu reaction to prepare aziridine **196**. The resolution of (±)-**207** *via* chiral HPLC is a major contributing factor to the very low overall yield, and an asymmetric route would be desirable to increase the throughput.

3.11.4. Fourth Generation Synthesis of Oseltamivir via a Barium-Catalyzed Asymmetric Diels–Alder Type Reaction

The Shibasaki group has recently reported a fourth generation approach to oseltamivir that, as the third generation, sets the stereochemistry of two of the chiral centers on the molecule *via* an asymmetric, barium-catalyzed Diels–Alder-type reaction (Scheme 24).[75] Diene 1-(trimethylsiloxy)-1,3-butadiene (**199**) and dienophile dimethyl fumarate (**210**) were chosen as the substrates for this transformation. Even though siloxy dienes, such as Danishefsky's diene, have been employed in the past in Lewis acid-catalyzed asymmetric Diels–Alder reactions,[88] the authors highlighted the fact that **199** has never been used before in this type of transformation due to its acid lability. A considerable amount of optimization was performed to develop a conceptually different catalytic, asymmetric Diels–Alder-type reaction that did not rely on acid catalysis. Thus, several metal isopropoxides were tested

(Mg, Ba, Sc, Gd) in combination with chiral ligands **221**, **222**, and **223**–**225**[89] (Figure 8) and additives (KF, LaF$_3$, ZnF$_2$, CsF). The best results were obtained with Ba(Oi-Pr)$_2$ (2.5 mol %), ligand **225** (2.5 mol %), and CsF (2.5 mol %) in THF (0.2 M) at −20 °C, which provided a mixture of adducts **211/212** (d.r. 5:1) in 91% yield and 95% ee (**211**), even on a 58-g scale. In this same publication, the authors also proposed a catalytic cycle for this transformation.

Once the conditions for the asymmetric Diels–Alder reaction had been developed, the synthesis continued with the hydrolysis of the methyl esters to afford a mixture of diacids **213** and **214**, which, upon reaction with DPPA[90] and TEA, generated diacyl azide **203**. During this transformation, the temperature had to be maintained below 4 °C to avoid spontaneous Curtius rearrangement and the resulting product loss. In addition, the products derived from **212** decomposed and only diastereomer **203** was obtained in excellent yield after chromatography. The treatment of **203** with anhydrous *tert*-BuOH at 80 °C produced cyclic carbamate **204** *via* a Curtius rearrangement and installed the two amino functionalities on the ring. This material could be obtained in enantiomerically pure form after recrystallization from CH$_2$Cl$_2$/ cyclopentyl methyl ether. The researchers mentioned that,
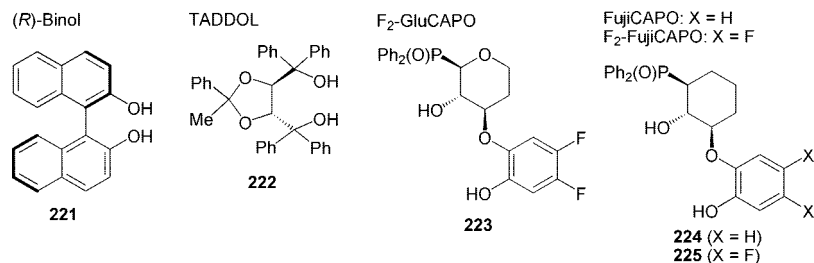
Figure 8. Chiral Ligands for the Asymmetric Diels−Alder Reaction between **199** and **210**

in order to avoid the isolation of potentially explosive **203**, an optimized protocol was developed which consisted of performing an aqueous workup after the DPPA reaction to remove the byproducts from the reaction and adding the resulting EtOAc solution of **203** to *tert*-BuOH and subsequent heating. Carbamate **204** was then acetylated to provide intermediate **215**, which, upon treatment with protected hydroxy malononitrile **216**[91] in the presence of $[Pd_2(dba)_3] \cdot CHCl_3$ and 4 mol % of dppf in toluene at 60 °C, underwent regioselective allylic substitution to provide intermediate **217**. This alkene was then epoxidized with trifluoroperacetic acid[92] to provide exclusively epoxide **218** as a result of the directing effect of the acetamido group at carbon 4. The conversion of the acetoxydicyanomethyl group to an ethoxycarbonyl group[91] and subsequent E2 epoxide opening were carried out with ethanolic K_2CO_3 to give alcohol **219**. The derivatization of alcohol **219** to the corresponding triflate, mesylate, chloride, or cyclic sulfamidate to introduce the 3-pentyloxy group *via* S_N2 inversion was not successful, and an alternative approach was pursued. Thus, the stereochemistry of the hydroxy group was inverted under Mitsunobu conditions, and the resulting diastereomeric alcohol **220** underwent a second Mitsunobu reaction to generate aziridine **144**, which is one of the intermediates found in Corey's synthesis of oseltamivir.[64] Some optimization was required to produce **144** under Mitsunobu conditions, and it was found that the choice of phosphine had a major impact on the outcome, since, with phosphines other than Me_2PPh, oxazoline **226** was obtained as the major product (Figure 9). The synthesis of oseltamivir phosphate

226
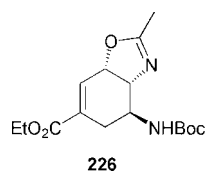
Figure 9. Major product from the second Mitsunobu reaction with phosphines other than Me_2PPh.

was completed by treating aziridine **144** with 3-pentanol in the presence of $BF_3 \cdot Et_2O$ to provide intermediate **131**, followed by Boc-protecting group removal with TFA and final H_3PO_4 salt formation.

This last approach to oseltamivir by Shibasaki's group differs from the previous three in that the chirality is introduced in the molecule in the first step through an asymmetric Diels−Alder reaction of two commercially available materials in the presence of a chiral ligand developed in this same group. A low catalyst loading is a clear advantage as well. In addition, an interesting methodology for the introduction of the ester group on the cyclohexene ring has been disclosed through the use of malononitrile **216**. The overall yield has also been improved considerably. At

the same time, some transformations from previous syntheses have been maintained, such as the azide chemistry and the subsequent high temperature Curtius rearrangement and the Mitsunobu reaction for aziridine formation. The authors highlighted the fact that, since most intermediates are crystalline, the use of chromatographic purifications could be minimized. It is possible that, with some optimization, this route may have the potential to become a scalable process

3.12. Synthesis of a Functionalized Cyclohexene Skeleton of Oseltamivir *via* Ring-Closing Metathesis by Yao's Group

The group of Yao at the Shanghai Institute of Organic Chemistry has reported the synthesis of cyclohexene **248**, which possesses the desired functionality and stereochemistry found in oseltamivir, *via* a ring-closing metathesis protocol (Scheme 25).[93] Compound **248** only differs from oseltamivir in that it lacks the 2-pentyl ether functionality. Unlike some previous syntheses that employed (−)-quinic or (−)-shikimic acids, this route starts from inexpensive L-serine (**227**), which was transformed to the known alkene **229** according to published protocols.[94,95] The double bond was dihydroxylated to give diol **230**, whose amino group was deprotected through hydrogenolysis in the presence of 20% $Pd(OH)_2/C$ to generate amine **231**. The authors highlighted the fact that all attempts to selectively remove the *N*-PMB group in the presence of the Cbz group failed. The amino group and the terminal hydroxyl group were protected and the secondary alcohol was oxidized under Swern conditions to afford ketone **234**, which underwent Wittig olefination[96] to provide alkene **235**. The *N,O*-acetal was selectively deprotected with catalytic $BiBr_3$,[97] and the primary alcohol was oxidized under Swern conditions to produce aldehyde **237**. The addition of vinylmagnesium bromide in the presence of stoichiometric $ZnCl_2$[98] gave a mixture of the desired *anti*- (**238**, 56%) and undesired *syn*-adducts (**239**, 19%). The relative stereochemistry of these two adducts was determined through derivatization to cyclohexenes **249** and **250** (Scheme 26) and NOESY experiments. The major *anti*-adduct **238** was shown to have the same absolute stereochemistry as the cyclohexene ring of oseltamivir. The synthesis continued with the protection of the hydroxy group in **238** as the MOM ether and subsequent ring-closing metathesis in the presence of the second-generation Grubbs catalyst **252** (Figure 10) to give cyclohexene **241**. Lower yields were obtained when the first generation catalyst **251** was employed. The TBDPS protecting group was removed with TBAF, and the hydroxy group was oxidized to acid **244** in a two-step sequence.[99] The acid was esterified with ethanol in the presence of EDCI to give ester **245**. The synthesis of **248** was completed through the removal of the MOM-protecting group under

Scheme 25. Yao's Group Synthesis of Precursor 248 to Oseltamivir
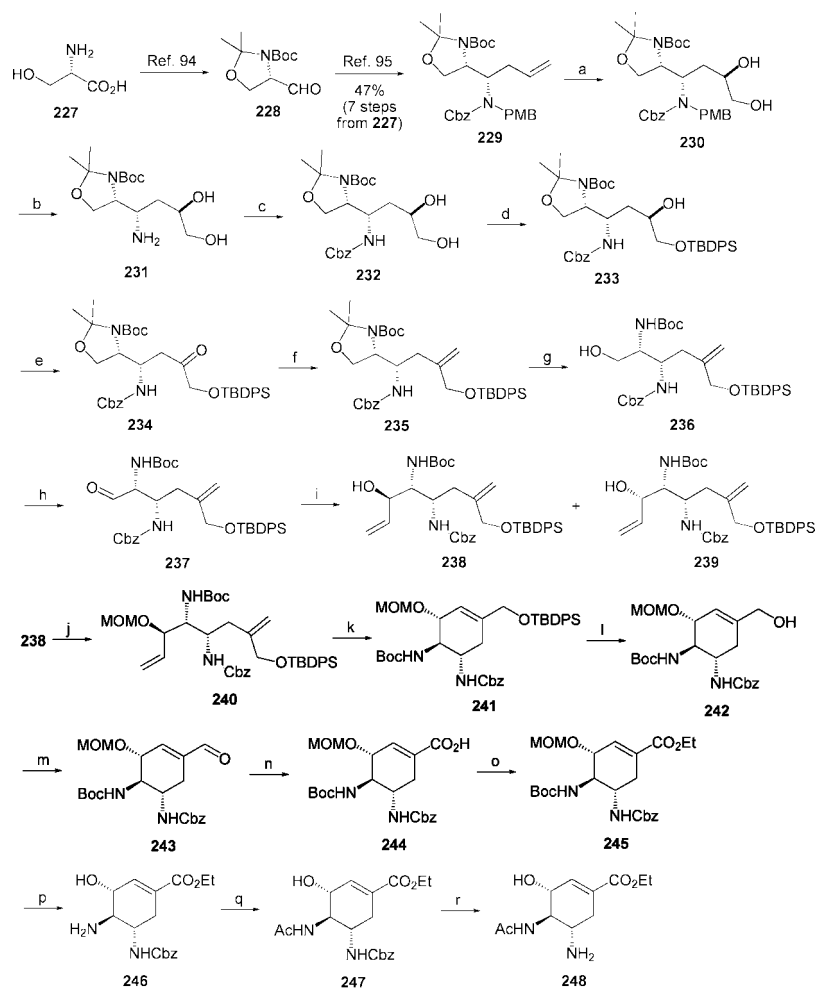
Reagents and conditions: (a) OsO$_4$, NMO, acetone/H$_2$O 5:1, 89%. (b) H$_2$, Pd(OH)$_2$, MeOH, 35 °C. (c) CbzCl, NaHCO$_3$, H$_2$O/EtOAc (v/v = 1:1), 86% (2 steps). (d) TBDPSCl, imidazole, CH$_2$Cl$_2$, rt, 96%. (e) (COCl)$_2$, DMSO, CH$_2$Cl$_2$, TEA, -78 °C. (f) Ph$_3$PCH$_3$Br, n-BuLi, THF, -78 °C to rt, 86% (2 steps). (g) BiBr$_3$ (20 mol%), MeCN, rt, 89%. (h) (COCl)$_2$, DMSO, CH$_2$Cl$_2$, TEA, -78 °C. (i) VinylMgBr (3 eq.), ZnBr$_2$ (1 eq.), THF, -78 to -30 °C, **238** (56%) + **239** (19%). (j) MOMCl, DIPEA, CH$_2$Cl$_2$, rt, 98%. (k) **252** (10 mol%), CH$_2$Cl$_2$, rt, 98%. (l) TBAF, THF, rt, 96%. (m) PCC, 4 Å mol. sieves, CH$_2$Cl$_2$, rt. (n) NaClO$_2$, K$_2$HPO$_4$, 2,3-dimethylbuta-1,3-diene, t-BuOH/THF/H$_2$O (v/v/v 4:1:1), 10 °C to rt, 88% (2 steps). (o) EtOH, HOBt, EDCI, DIPEA, CH$_2$Cl$_2$, rt, 85%. (p) 5% HCl/EtOH, 0 °C to rt. (q) AcCl, Na$_2$CO$_3$, EtOH, 0 °C to rt, 83% (2 steps). (r) Pd(OAc)$_2$, Et$_3$SiH, TEA, CH$_2$Cl$_2$, 0 °C to rt, 92%.

Scheme 26. Derivatization of Dienes 238 and 239
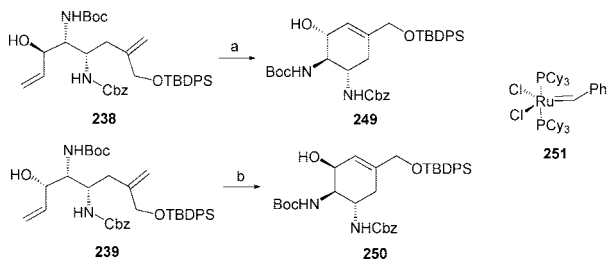
Reagents and conditions: (a) **251** (10 mol%), CH$_2$Cl$_2$, rt, 77%. (b) **251** (10 mol%), CH$_2$Cl$_2$, rt, 70%.

acidic conditions, the acetylation of the amino group, and the removal of the Cbz-protecting group under Pd-catalyzed reductive conditions.[100] The overall yield for this synthetic route was 19% from intermediate **229**.
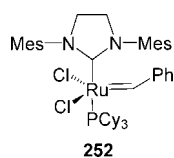
Figure 10. Ring-closing metathesis catalyst employed in the synthesis of **241**.

The major advantage of Yao's synthesis is that it starts with readily available L-serine instead of with the more commonly used (−)-quinic or (−)-shikimic acids. The researchers assembled a highly functionalized substrate (**240**), which contained all the desired stereochemistry, before carrying out the key ring-closing metathesis transformation in almost quantitative yield with Grubbs second generation catalyst. This is the only example to date where this powerful reaction has been employed to generate oseltamivir. Even though this is a very long route (25 steps), in part because of extensive protecting group manipulation, the overall yield is excellent (8%). Many of the intermediates are purified by flash chromatography, and only milligram quantities of the drug were produced, which, together with the cost of goods, would make this route difficult to implement on a large scale.

3.13. Synthesis of Oseltamivir Phosphate via an Asymmetric Diels−Alder Reaction by Fukuyama's Group

The group of Fukuyama at the University of Tokyo has reported a new synthetic approach to oseltamivir that, as do Corey's[64] and Shibasaki's[75] syntheses, employs an asymmetric Diels−Alder reaction to introduce the chirality in the

Scheme 27. Fukuyama's Group Synthesis of Oseltamivir Phosphate
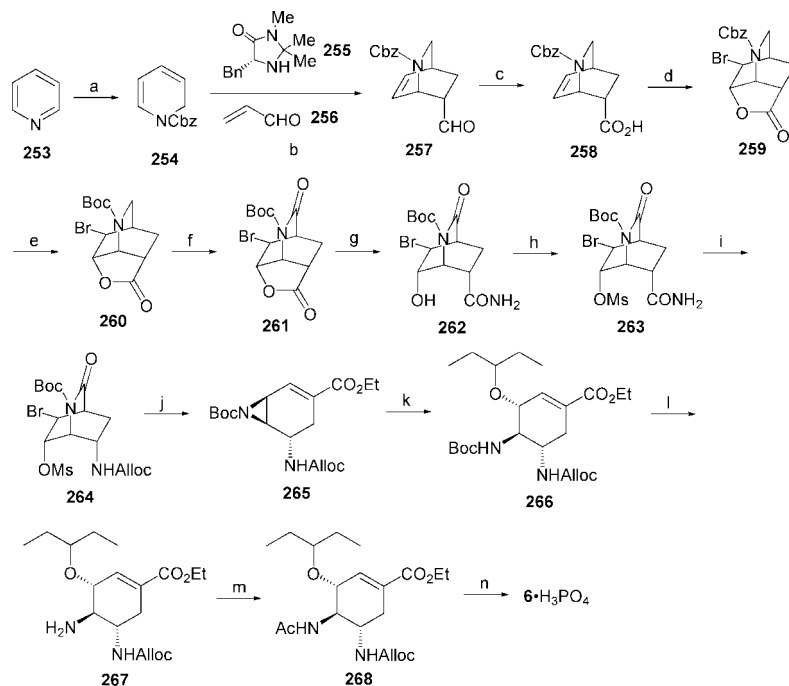
Reagents and conditions: (a) NaBH$_4$, CbzCl, MeOH, -50 to -35 °C, 1 h. (b) Acrolein (**256**), **255** (10 mol%), MeCN, H$_2$O, rt, 12 h. (c) NaClO$_2$, NaHPO$_4$·2H$_2$O, 2-methyl-2-butene, t-BuOH, H$_2$O, 0 °C to rt, 1 h. (d) Br$_2$, NaHCO$_3$, CH$_2$Cl$_2$, H$_2$O, rt, 26% (4 steps). (e) H$_2$, Pd/C, Boc$_2$O, EtOH, THF, rt, 2 h, 92%. (f) RuO$_2$·nH$_2$O (10 mol%), NaIO$_4$, ClCH$_2$CH$_2$Cl, H$_2$O, 80 °C, 1.5 h, 86%. (g) NH$_3$, t-BuOH, THF, 0 °C, 95%. (h) MsCl, TEA, CH$_2$Cl$_2$, rt, 1 h, 91%. (i) allyl alcohol, PhI(OAc)$_2$, mol. sieves (4 Å), toluene, 60 °C, 10 h, 88%. (j) NaOEt, EtOH, 0 °C, 87%. (k) 3-Pentanol, BF$_3$·OEt$_2$, -20 °C, 62%. (l) TFA, CH$_2$Cl$_2$, 0 °C to rt. (m) Ac$_2$O, py, 88% (2 steps). (n) (i) Pd/C, Ph$_3$P, 1,3-dimethylbarbituric acid, EtOH, reflux, 40 min; (ii) H$_3$PO$_4$, 76% (2 steps).

cyclohexene ring (Scheme 27).[101] The synthesis started with the reduction of pyridine (**253**) with NaBH$_4$ in the presence of CbzCl to afford dihydropyridine **254**.[102] Since the asymmetric Diels−Alder reaction between dihydropyridine derivatives and acrylic acid derivatives is a methodology that is not developed enough to be useful in synthesis,[103] the researchers opted for a two-step approach to solve this problem. First, the asymmetric Diels−Alder reaction carried out between diene **254** and acrolein (**256**) as dienophile with MacMillan's catalyst **255**[104] provided a mixture of aldehydes that contained the desired aldehyde **257**. No information was provided by the researchers on the enantioselectivity of this transformation. Since the separation of the different components of this mixture was impractical, in the second step this unpurified mixture was subjected to Kraus oxidation[105] with NaOCl$_2$ to give a mixture of acids that contained the desired acid **258**. After removing the basic impurities, the acid mixture underwent bromolactonization to provide bromide **259** as one of the products. This intermediate could be purified by recrystallization from MeOH to afford material with >99% ee without resorting to chromatography. After removing the Cbz-protecting group and reprotecting with Boc$_2$O,[106] the resulting lactone **260** was oxidized with NaIO$_4$ and a catalytic amount of RuO$_2$·nH$_2$O to generate imide **261**. The treatment of **261** with ammonia, followed by the mesylation of the resulting alcohol, provided amide **263**, which was subjected to Hofmann rearrangement in the presence of iodobenzene diacetate and allyl alcohol to give carbamate **264**.[107] The treatment of **264** with sodium ethoxide caused the ethanolysis of the lactam, the elimination of HBr, and the subsequent aziridine formation to produce intermediate **265**. The opening of the aziridine ring in **265** with 3-pentanol, followed by the removal of the Boc-protecting group and acetylation of the resulting amine with Ac$_2$O, led

to the formation of acetamide **268**. The alloc-protecting group was removed under reductive conditions, and the addition of H$_3$PO$_4$ to the resulting amine completed the preparation of oseltamivir phosphate.

The overall yield for this synthetic route was 5.6% from pyridine and 22% from bromolactone **259**. The authors highlighted the fact that, even though the yield for the preparation of **259** from pyridine is only 26%, this compound is crystalline and it can be easily purified. Also, the chirality is introduced early in the synthesis, it is an azide-free process, and many steps do not require chromatographic separation. If the protecting group strategy could be simplified to reduce the number of transformations and the catalyst loading and efficiency of the asymmetric Diels−Alder reaction were optimized, this route could potentially be amenable for scale-up.

3.14. Synthetic Approaches to Oseltamivir by Fang's Group

3.14.1. Synthesis of Oseltamivir Phosphate from D-Xylose

A collaboration between the Academia Sinica in Taiwan, the Chemistry Department at the National Taiwan University, and the Skaggs Institute of Chemical Biology generated a new synthetic route to oseltamivir starting from D-xylose (Scheme 28).[108] This approach also provided access to the phosphonate congeners of oseltamivir for biological studies, since the phosphonate group can be employed as a bioisostere of the carboxylate group in drug design. The synthetic route started from 1,2-O-isopropylidene-α-D-xylofuranose (**269**), prepared from D-xylose in one step and 96% yield according to a published procedure,[109] which was treated with pivaloyl chloride to generate intermediate **270**. Alcohol oxidation,

Scheme 28. Synthesis of Oseltamivir from 1,2-*O*-Isopropylidene-α-D-xylofuranose (269) by Fang's Group
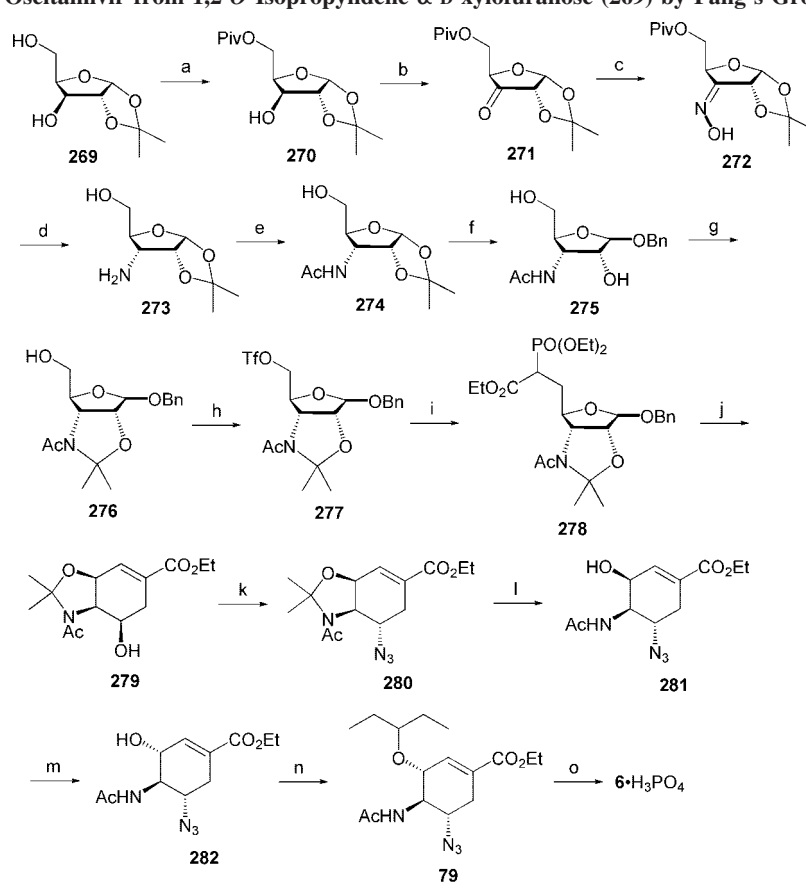
Reagents and conditions: (a) PivCl, py, 0 °C, 8 h, 89%. (b) PDC, Ac$_2$O, reflux, 1.5 h. (c) HONH$_2$•HCl, py, 60 °C, 24 h, 82%. (d) LiAlH$_4$, THF, 0 °C to reflux, 1.5 h, 88%. (e) Ac$_2$O, py, 25 °C, 3 h. (f) Benzyl alcohol, 4 M HCl in dioxane, PhMe, 0 to 25 °C, 24 h, α/β = 7:3, 85% (2 steps). (g) 2,2'-Dimethoxypropane, *p*-TsOH, PhMe, 80 °C, 4 h, 90%. (h) Tf$_2$O, py, CH$_2$Cl$_2$, -15 °C, 2 h. (i) Triethyl phosphonoacetate, NaH, 15-crown-5, DMF, 25 °C, 24 h, 80%. (j) (i) H$_2$, Pd/C, EtOH, 25 °C, 24 h; (ii) NaH, THF, 25 °C, 1 h, 83%. (k) DPPA, DIAD, Ph$_3$P, THF, 25 °C, 48 h. (l) HCl, EtOH, reflux, 1 h, 93% (2 steps). (m) (i) Tf$_2$O, py, CH$_2$Cl$_2$, -15 to -10 °C, 2 h; (ii) KNO$_2$, 18-crown-6, DMF, 40 °C, 24 h, 70%. (n) Cl$_3$CC(=NH)OCHEt$_2$, CF$_3$SO$_3$H, CH$_2$Cl$_2$, 25 °C, 24 h, 78%. (o) (i) H$_2$, Lindlar's catalyst, EtOH, rt, 16 h; (ii) H$_3$PO$_4$, EtOH, 40 °C, 1 h, 91% (2 steps).

reaction of the resulting ketone with hydroxylamine hydrochloride, and reduction of the oxime with LiAlH$_4$ afforded aminoalcohol **273**. The amino group was acetylated to give acetamide **274**, which underwent reaction with benzyl alcohol under acidic conditions to provide ribofuranoside **275** as a mixture of anomers (α/β = 7:3). The treatment of **275** with 2,2-dimethoxypropane afforded *N,O*-ketal **276** in the same anomeric α/β ratio. This alcohol mixture was converted to triflate **277**, and this group was displaced with triethyl phosphonoacetate to give phosphoryl ester **278**. The stage was then set for the subsequent intramolecular Horner–Wadsworth–Emmons reaction, which was carried out with NaH as base and catalytic 15-crown-5 to provide cyclohexene **279**. A Mitsunobu reaction installed the azido group,[110] and subsequent acid treatment deprotected the amino and hydroxy groups to generate azide **281**. After inverting the stereochemistry of the hydroxy group, the resulting alcohol was treated with 3-pentyl trichloroacetimidate to introduce the 3-pentyl ether functionality. Finally, azide reduction and the addition of H$_3$PO$_4$ completed the synthesis of oseltamivir phosphate.

This first synthesis of oseltamivir by Fang's group has the advantage of starting from very inexpensive and readily available D-xylose, and after 16 steps, the 15% overall yield is excellent. It features some steps that depart from previous approaches to accomplish certain transformations, such as a

novel methodology for the preparation of the 2-pentyl ether functionality that avoids the traditional and somewhat problematic aziridine-opening by 3-pentanol, an oxime reduction protocol to introduce the amino group at carbon 4, and, finally, a hydroxy group inversion method without resorting to Mitsunobu chemistry. Some of the drawbacks are extensive protecting group manipulation, the use of DPPA to introduce the amino group at carbon 5, and the need for chromatography to purify most intermediates. This synthetic route has been demonstrated on a milligram scale.

3.14.2. Synthesis of Oseltamivir Phosphate from Chiral cis-1,2-Dihydrodiol 283

Fang's group at the National Taiwan University has recently reported a second approach to oseltamivir from enantiopure bromodiol **283** (Scheme 29) as well as the preparation of Tamiphosphor, an oseltamivir analogue in which the ester group has been replaced by a phosphonate group.[111]

The synthesis of oseltamivir started from commercially available **283**, which can be obtained on a large scale by microbial oxidation of bromobenzene.[112] This material was first protected as the acetonide followed by a SnBr$_4$-catalyzed bromoacetamidation[113] to afford intermediate **285** regio- and stereoselectively. The structure of this compound was

Scheme 29. Synthesis of Oseltamivir from Enantiopure Bromodiol 283 by Fang's Group
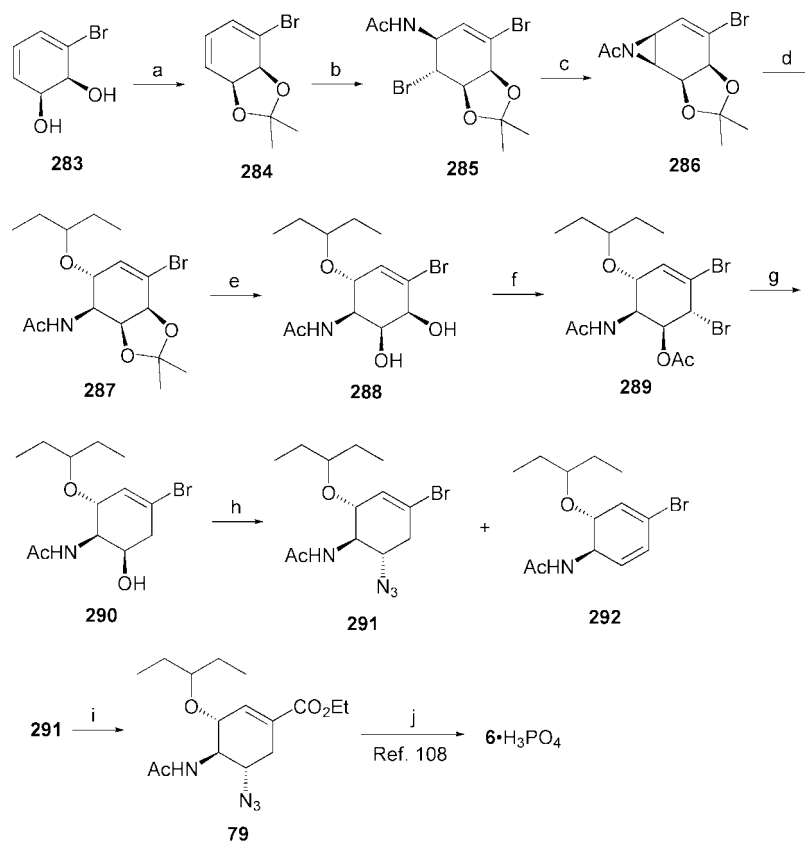
Reagents and conditions: (a) Dimethoxypropane, p-TsOH•H$_2$O, acetone, 0 °C to rt, 30 min; (b) SnBr$_4$ (cat.), N-bromoacetamide, MeCN/H$_2$O, 0 °C, 8 h, 75% (2 steps); (c) LiHMDS, THF, -10 to 0 °C, 30 min; (d) 3-Pentanol, BF$_3$•OEt$_2$, -10 to 0 °C, 6 h, 73% (2 steps); (e) cc HCl, MeOH, 50 °C, 6 h, 94%; (f) AcOCMe$_2$COBr, THF, 0 °C to rt, 3.5 h; (g) LiBHEt$_3$, THF, 0 °C to rt, 2 h, 82% (2 steps); (h) DPPA, DIAD, PPh$_3$, THF, 40 °C, 24 h, 84% (**291**) and 2% (**292**); (i) [Ni(CO)$_2$(PPh$_3$)$_2$], DIPEA, EtOH, THF, 80 °C, 24 h, 81%; (j) (i) H$_2$, Lindlar catalyst; (ii) H$_3$PO$_4$, EtOH, 50 °C, 6 h, 91% (2 steps).

confirmed by X-ray diffraction analysis. The stereochemical outcome was rationalized *via* the formation of a bromonium ion on the less hindered face of the ring with subsequent backside attack of the acetamide moiety at the allylic carbon 5 position. The treatment of **285** with LiHMDS provided aziridine **286**, which, in the presence of 3-pentanol and BF$_3$•OEt$_2$ as catalyst, afforded ether **287**. The acetonide was cleaved under acidic conditions, and the resulting diol was treated with α-acetoxyisobutyryl bromide to give dibromide **289**. The acetyl group and the bromine atom at the allylic position were reduced with LiBHEt$_3$ to generate alcohol **290**, which underwent a Mitsunobu reaction with diphenylphosphoryl azide[108] to produce azide **291** and a small amount (2%) of diene **292** after water elimination. The introduction of the necessary ester functionality was accomplished *via* the reaction of **291** with [Ni(CO)$_2$(PPh$_3$)$_2$] in the presence of ethanol.[114] The completion of the synthesis of oseltamivir phosphate was carried out as has been previously reported.[108]

This second approach to oseltamivir by Fang's group cleverly takes advantage of the chirality already present in diol **283** to accomplish its goal. In spite of the fact that it involves azide chemistry and, probably, high cost of goods, this short (11 steps) and very high-yielding route (26%) shows a lot of potential to produce large quantities of drug, since many intermediates are crystalline, and according to the authors, the isolation procedures were relatively simple and cost-effective.

Scheme 30. Azide-free synthesis of oseltamivir from alcohol 290 by Fang's group
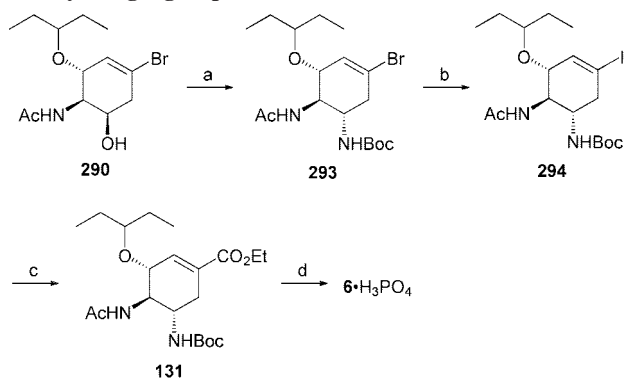
Reagents and conditions: (a) (i) DDQ, PPh$_3$, n-Bu$_4$NOCN, MeCN, rt, 18 h; (ii) *tert*-BuOH, reflux, 24 h, 78% (2 steps). (b) CuI, KI, N,N'-dimethylethylenediamine, n-BuOH, 120 °C, 24 h. (c) Pd(OAc)$_2$, CO, NaOAc, EtOH, rt, 24 h, 82% (2 steps). (d) H$_3$PO$_4$, EtOH, 50 °C, 6 h, 81%.

In the same publication, an azide-free synthesis of oseltamivir was also reported from alcohol **290** (Scheme 30). The amine functionality was introduced through the reaction with tetrabutylammonium cyanate in the presence of triphenylphosphine and DDQ to provide an isocyanate intermediate[115] that was treated with *tert*-butanol to provide Boc-protected amine **293**. Since the direct carbonylation of **293** was unsuccessful, the bromide functionality was converted to the corresponding iodide **294**,[116] which underwent pal-

Scheme 31. Synthesis of Oseltamivir Based on Cationic Iron Carbonyl Chemistry by Kann's Group

Reagents and conditions: (a) Fe$_2$(CO)$_9$, PhMe, 55 °C, 86%. (b) Ph$_3$CPF$_6$, CH$_2$Cl$_2$, rt, 94%. (c) **298**, DIPEA, CH$_2$Cl$_2$, 0 °C, 75%. (d) Preparative HPLC, 47% yield for **300**. (e) HPF$_6$, Et$_2$O, 0 °C, 94%. (f) Boc-NH$_2$, DIPEA, CH$_2$Cl$_2$, 0 °C, 86%. (g) H$_2$O$_2$, NaOH, EtOH, 0 °C, 95%. (h) m-CPBA, CH$_2$Cl$_2$, -70 °C to rt, 95%. (i) NaN$_3$, NH$_4$Cl, DME/EtOH/H$_2$O, 0 °C, 95%. (j) MsCl, TEA, CH$_2$Cl$_2$, 0 °C. (k) (i) Ph$_3$P, TEA, THF/H$_2$O, rt; (ii) Ac$_2$O, py, CH$_2$Cl$_2$, 0 °C, 65%. (l) 3-Pentanol, Cu(OTf)$_2$, 0 °C, 48%.
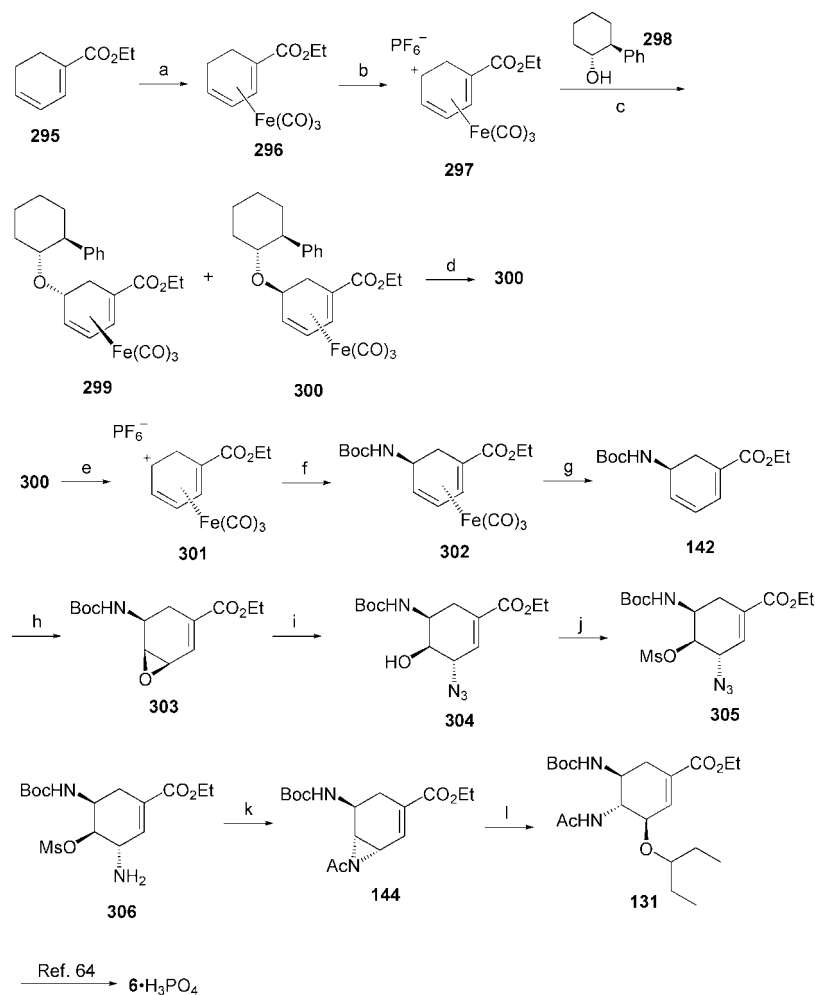
ladium-catalyzed carbonylation in ethanol to give ethyl ester **131**.[117] The one-pot Boc-deprotection and salt formation with phosphoric acid in ethanol provided oseltamivir phosphate.

This azide-free preparation of oseltamivir phosphate almost accomplishes the same high-yield found in the nonazide free route (26% vs 22%, respectively) and does not add any extra steps. The introduction of the ester group *via* either a nickel- or palladium-catalyzed carbonylation reaction is also a novel strategy not seen in previous syntheses. These further improvements in the entire process make Fang's contributions highly valuable toward an efficient large-scale route to oseltamivir.

3.15. Iron Carbonyl Approach to Oseltamivir Phosphate by Kann's Group

Researchers at Chalmers University of Technology and AstraZeneca in Sweden have developed a methodology for the synthesis of oseltamivir that is based on cationic iron carbonyl chemistry (Scheme 31).[118] The ability of this type of cationic complexes to react with a wide variety of nucleophiles make them attractive building blocks to generate new carbon–carbon and carbon–heteroatom bonds.[119] Furthermore, after oxidative decomplexation, the diene func-

tionality is available for further manipulations and this methodology has been exploited for the synthesis of natural products.[120]

The synthesis started with the formation of an iron carbonyl cation, based on previously published work on methyl cyclohexadienecarboxylate tricarbonyliron complexes.[121] Thus, cyclohexadienoic acid ethyl ester **295**, prepared from acrolein and the phosphonium salt of 4-bromobut-2-enoic acid ethyl ester in a tandem Michael/Wittig reaction,[122] was treated with diiron nonacarbonyl in toluene at 55 °C to provide racemic complex **296**. This complex underwent hydrogen abstraction with Ph$_3$CPF$_6$ to produce salt **297**. The researchers highlighted the fact that complexes like **296** as their corresponding acids can be resolved through the formation of a diastereomeric salt with a chiral amine,[123] but in this case they opted for a more efficient way which consisted in the preparation of diastereomeric complexes **299** and **300**, which could be separated by preparative HPLC. After several chiral alcohols were screened, the best results were obtained with (−)-(1R,2S)-trans-2-phenylcyclohexanol (**298**), which provided the diastereomeric mixture in 75% yield. Salt **301** was formed after treating diastereomer **300** with HPF$_6$, and at this point, the valuable chiral alcohol could also be recovered. The synthesis continued with the reaction

Scheme 32. Synthesis of Oseltamivir *via* Pd-Catalyzed Asymmetric Allylic Alkylation by Trost's Group
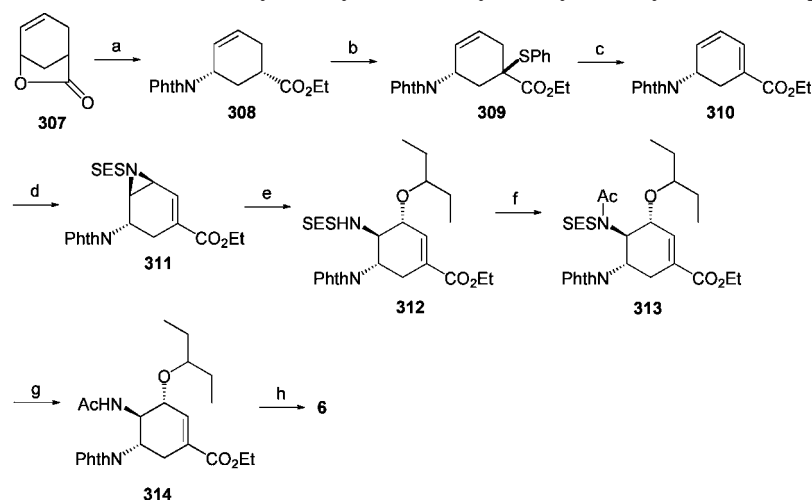
Reagents and conditions: (a) (i) [(η^3-C$_3$H$_5$PdCl)$_2$] (2.5 mol%), **315** (7.5 mol%), trimethylsilylphthalimide, THF, 40 °C; (ii) TsOH•H$_2$O, EtOH, reflux, 84%, 98% ee. (b) KHMDS, PhSSO$_2$Ph, THF, -78 °C to rt, 94%. (c) (i) *m*-CPBA, NaHCO$_3$, 0 °C; (ii) DBU, PhMe, 60 °C, 85%. (d) **316** (2 mol%), 2-(trimethylsilyl)ethanesulfonamide (SESNH$_2$), PhI(O$_2$CCMe$_3$)$_2$, MgO, PhCl, 0 °C to rt, 86%. (e) 3-Pentanol, BF$_3$•OEt$_2$, 75 °C, 65%. (f) DMAP, py, Ac$_2$O, MW, 150 °C, 1 h, 84%. (g) TBAF, THF, rt, 95%. (h) NH$_2$NH$_2$, EtOH, 68 °C, 100%.

between **301** and BOC-amine to generate intermediate **302**.[124] Anhydrous and inert conditions as well as slow addition of the base were critical to obtain good yields in this step. The decomplexation step to liberate the diene was performed with a combination of H$_2$O$_2$ and NaOH as base.[125] Selective epoxidation of the most electron rich alkene and opening of the epoxide with sodium azide afforded azido alcohol **304**. The selectivity of the epoxidation step was attributed to the directing effect of the carbamate group.[126] The hydroxyl group was mesylated, and the azido group was reduced to give amine **306**. Acetylation and concomitant aziridine formation produced intermediate **144**, which was converted to oseltamivir phosphate as has been previously shown.[64]

This route allowed for the preparation of oseltamivir phosphate in 14 steps from ester **295** in 5% overall yield. A clear advantage of this unusual approach is the potential for introducing different substituents on the ring, and thus it lends itself to the convenient generation of analogues for SAR studies. The use of unsafe reagents such as NaN$_3$ and *m*-CPBA, the lack of evidence that this type of chemistry can be scaled up, and the need for HPLC separation of diastereomers makes this approach a less likely candidate for the manufacture of large quantities of drug. As mentioned before, it should find an important niche in the Medicinal Chemistry area, where the production of a large number of analogues for biological testing is crucial.

3.16. Synthesis of Oseltamivir *via* a Novel Palladium-Catalyzed Asymmetric Allylic Alkylation Reaction by Trost's Group

Trost has reported a short synthesis of oseltamivir that relies on two key reactions: a novel palladium-catalyzed asymmetric allylic alkylation (Pd-AAA) to desymmetrize commercially available lactone **307** and a rhodium-catalyzed aziridination to install the acetamido group on the ring (Scheme 32).[127] The synthesis started with the desymmetrization of **307** through the use of commercially available trimethylsilylphthalimide as the nucleophile, [(η^3-C$_3$H$_5$PdCl)$_2$] as catalyst, and Trost ligand (*R,R*)-**315**. The use of other imide nucleophiles such as NHBoc$_2$, NHCbz$_2$,

NH(CHO)$_2$, or phthalimide failed to give any Pd-AAA in both the presence or absence of bases. Trimethylsilylphthalimide, on the other hand, gave very good yield and excellent steroselectivity. The authors suggested that this reagent, besides performing the Pd-AAA reaction, also trapped the carboxylate anion as it was being generated, thus avoiding the conversion of the cationic intermediate back into starting material. At the same time, it revealed the imide anion for nucleophilic attack. The trimethylsilyl group was cleaved and the resulting acid was esterified in a one-pot process to give ethyl ester **308**. The sulfenylation of **308** with PhSSO$_2$Ph afforded a 1:1 mixture of diastereomers of thioester **309**,[128] which was oxidized with *m*-chloroperbenzoic acid to the corresponding sulfoxide followed by thermal elimination to provide diene **310**. The regioselectivity of the elimination reaction was improved by the addition of DBU, but some of the 1,4-diene was also obtained (10:1 ratio). The aziridination step proved to be more difficult than expected, and extensive optimization was required. Copper catalysts showed little discrimination between the two double bonds. Silver and gold catalysts gave exclusively the desired aziridine **311**, but they displayed low reactivity.[129] Preliminary work with rhodium catalysts, which proceeds through a nitrene species generated *in situ*, gave the ring-opened product.[130] This problem was solved by both the selection of an stabilizing group on the aziridine that could be easily removed and the right choice of Rh catalyst. Thus, the 2-(trimethylsilyl)ethanesulfonyl (SES) protecting group was chosen together with catalyst **316**,[131] and these conditions provided aziridine **311** in excellent yield. Catalyst **316** (Figure 11) gave better conversion compared to [Rh$_2$(O$_2$CCPh$_3$)$_4$], [Rh$_2$(O$_2$CCMe$_3$)$_4$], or [Rh$_2$(CF$_3$CONH)$_4$]. The combination of PhI(O$_2$CCMe$_3$)$_2$ and SESNH$_2$ was chosen as the nitrene source. The synthesis continued with the opening of the aziridine with 3-pentanol in the presence of BF$_3$•OEt$_2$ to give ether **312**. After acylation of **312** using a microwave reactor to speed up the process, the SES protecting group was removed by treatment with TBAF. The final step involved the cleavage of the phthalimido group with hydrazine to give oseltamivir **6**.
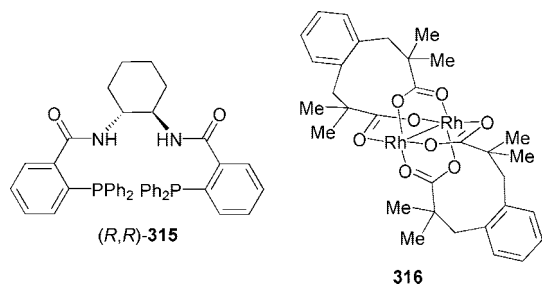
Figure 11. Structures of Trost ligand **315** for asymmetric allylic alkylation and Du Bois rhodium catalyst **316** for C−H insertion reaction.

This azide-free synthetic route required only eight steps from commercially available starting materials and proceeded in 30% overall yield, despite the fair yield of the aziridine-opening step. The use of MW radiation and hydrazine as well as the cost of goods are caveats of the synthesis when the scalability is brought into consideration. To date, this is the most concise synthesis of oseltamivir reported in the literature and offers a very different approach for the introduction of chirality on the molecule.

3.17. Chemoenzymatic Synthesis of Oseltamivir Phosphate from Chiral *cis*-1,2-Dihydrodiol 283 by Banwell's Group

Banwell's group at the Australian National University has recently reported a chemoenzymatic formal total synthesis of oseltamivir that, as in the second generation route by Fang's group,[111] also employs *cis*-1,2-dihydrodiol **283** as starting material (Scheme 33).[132] The synthesis started with the reaction between **283** and *p*-methoxybenzyl dimethoxyacetal in the presence of (+)-camphorsulfonic acid to give acetal **317** stereoselectively, which was reduced with DIBAL-H at low temperature to afford monoprotected diol **318** and its regioisomer in a 6:1 ratio. The reaction of **318** with hydroxylamine in the presence of CDI provided *N*-hydroxycarbamate **319**. This material could be separated from the PMB ether of *o*-bromophenol by chromatography, and its structure was confirmed by X-ray analysis. Tosylation of **319** followed by copper-catalyzed intramolecular aziridination[133] afforded carbamate **322**. The authors proposed that this intermediate was formed *via* the regioselective ring-opening of the highly strained acylaziridine **321** by 3-pentanol. Several copper catalysts were screened for the intramolecular aziridination step, and Cu(CH₃CN)₄PF₆ was found to be the best choice. Carbamate **322** was then hydrolyzed with aqueous lithium hydroxide at reflux, and the resulting amine **323** was acetylated to provide acetamide **324**. The authors highlighted that when **322** was first acetylated and then treated with base, no ring-opening was observed. After the removal of the PMB protecting group under acidic conditions, bromodiol **288** was obtained, which is one of the intermediates in the second generation route to oseltamivir by Fang's group.[111]

This enantioselective route is 14 steps long, and the overall yield is 6.2%. It accesses diol **288** through a more elaborated route than in Fang's approach (8 steps vs 5 steps, respectively) and the yield to this common intermediate is substantially lower (12% vs 51%), which makes Banwell's route less practical.

3.18. Synthetic Approaches to Oseltamivir Phosphate by Shi's Group

Shi's group at East China University of Science and Technology has reported two synthetic approaches to oseltamivir phosphate that rely on (−)-shikimic acid as starting material. The researchers highlighted the fact that this material is readily available either by extraction from the Chinese star anise (1 kg of shikimic acid/30 kg of dried plant) or through fermentation using genetically modified *Escherichia coli*.[134]

3.18.1. First Synthesis of Oseltamivir Phosphate from (−)-Shikimic Acid

The first synthesis by Shi's group is shown in Scheme 34.[135] The synthesis started with the conversion of (−)-shikimic acid (**42**) to alcohol **86**, as has been previously reported in high yield,[51] and subsequent treatment with benzoyl chloride to afford benzoyl acetonide **325**. The acetonide functionality was cleaved through treatment with aqueous HCl to give crystalline diol **326**, which underwent reaction with MsCl to generate bismesylate **327**. After a solvent (EtOAc, CH₂Cl₂, CHCl₃) and base (TEA, pyridine) screen was carried out, it was determined that EtOAc and pyridine were the solvent and base of choice, respectively, for this transformation. The selective displacement of the mesylate group at the carbon 3 position was accomplished by treating **327** with NaN₃ in aqueous DMF at low temperature to cleanly provide azide **328**. The authors attributed this selectivity to the higher reactivity of the allylic position as well as to the fact that this position is less sterically hindered than the C4 position (Figure 12). The azido group
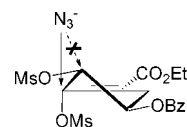
Figure 12. Rational for the regioselective displacement of mesylate at carbon 3 by azide.

was reduced with Ph₃P, and subsequent treatment with TEA provided aziridine **329**, which was acetylated with acetic anhydride to provide intermediate **330**. The aziridine opening step was performed regio- and stereoselectively with 3-pentanol and BF₃·Et₂O as Lewis acid at low temperature to generate acetamide **331** in excellent yield. The authors rationalized the regioselectivity of this transformation as before for the mesylate displacement with azide, which was attributed to the higher reactivity of the allylic position (Figure 13). The benzoyl group was cleaved with K₂CO₃ in
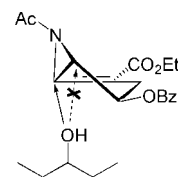
Figure 13. Rationale for the regioselective opening of aziridine **330** by 3-pentanol.

ethanol to provide alcohol **332**, which was mesylated under standard conditions, and the mesylate group was displaced with NaN₃ in hot, aqueous DMF to produce azide **79**. The hydrogenation of the azido group in the presence of Lindlar catalyst cleanly provided the corresponding amine intermedi-

Scheme 33. Formal Total Synthesis of Oseltamivir Phosphate from Bromodiol 283 by Banwell's Group
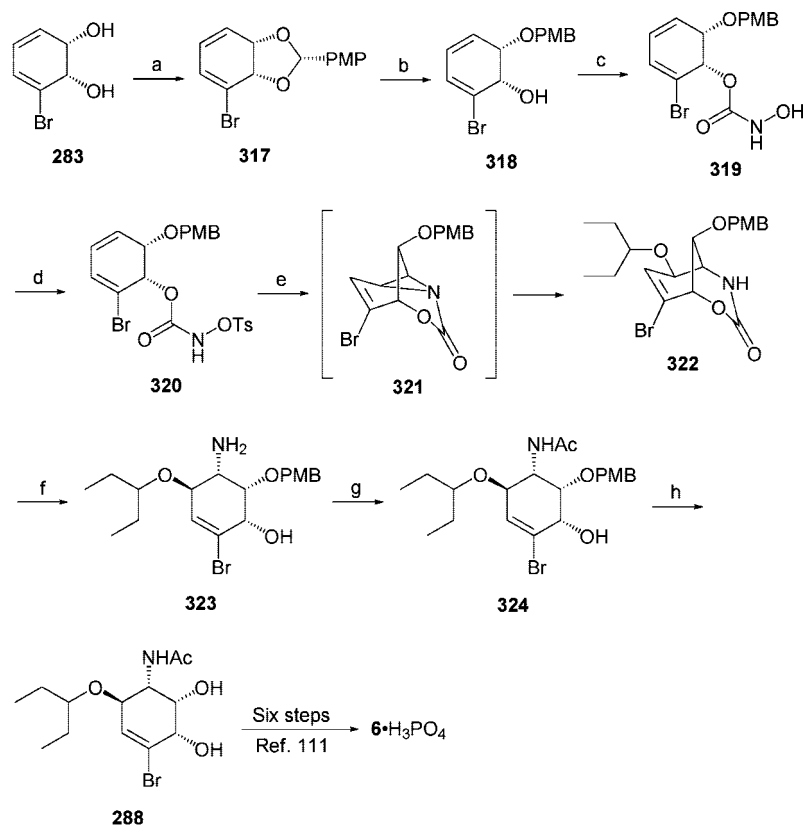
Reagents and conditions: (a) 4-methoxybenzaldehyde dimethyl acetal, (+)-camphorsulfonic acid, PhMe, 0 °C, 1.5 h. (b) DIBAL-H, TEA, PhMe, -78 °C to -30 °C, 5 h, 85% (2 steps). (c) (i) CDI, MeCN, 0 °C, 1 h; (ii) NH$_2$OH•HCl, imidazole, 0 °C to 18 °C, 16 h, 56% (at 88% conversion). (d) p-TsCl, TEA, Et$_2$O, 0 °C to 18 °C, 16 h, 79%. (e) Cu(MeCN)$_4$PF$_6$, K$_2$CO$_3$, MeCN, 3-pentanol, 0 °C to 18 °C, 16 h, 43%. (f) LiOH, 1,4-dioxane/water, 100 °C, 48 h, 85%. (g) AcCl, TEA, 0 °C to 18 °C, 1 h, 99%. (h) HCl, MeOH, 35 °C, 16 h, 90%.

ate. Ra−Ni also worked for this transformation, whereas Pd/C reduced the double bond as well. The use of Ph$_3$P as reducing agent gave lower yield. The addition of H$_3$PO$_4$ in an EtOAc/EtOH mixture completed the synthesis of oseltamivir phosphate.

This process required 13 steps to accomplish its goal and produced oseltamivir phosphate in 40% yield, the third highest-yielding synthesis to date after the second synthesis from this same group and Hayashi's (*vide infra*). Minimal protecting group manipulation and a very efficient aziridine-opening step with 3-pentanol are key factors for this outcome. Even though azide chemistry is used in two instances and several intermediates are purified by flash chromatography, overall it is a very efficient synthesis and, with some optimization, a good candidate for large scale production of the drug.

3.18.2. Optimized Synthesis of Oseltamivir Phosphate from (−)-Shikimic Acid

Shi's group built on the experience accumulated in the previous synthesis to develop a shorter and more efficient methodology to oseltamivir phosphate (Scheme 35).[136] Thus, (−)-shikimic acid was converted to triol **85** as has been previously shown.[51] After conversion to trimesylate **334**, the allylic mesylate group was selectively displaced with NaN$_3$ to provide intermediate **335** with complete inversion of stereochemistry at the carbon 3 of the ring. Low temperature was required to carry out this transformation successfully,

or otherwise, byproduct **338** was obtained after elimination and aromatization (Figure 14). The azido group reduction
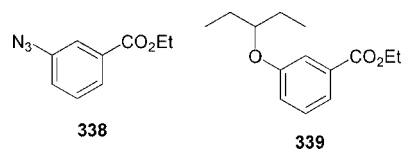
Figure 14. Aromatic byproducts from the displacement of mesylate groups by nitrogen nucleophiles.

with Ph$_3$P followed by the addition of TEA afforded aziridine **336**. The removal of the Ph$_3$PO byproduct could be performed by forming the HCl salt in aqueous media with NaHSO$_4$ and performing an organic solvent wash. Intermediate **336** was then acetylated and the resulting cyclic acetamide was regioselectively opened with 3-pentanol to generate ether **333**. This transformation proceeded with complete inversion of configuration at carbon 3 according to the Walden-type model and took advantage of the higher reactivity of the allylic position. The displacement of the last mesylate group with NaN$_3$ in an ethanol/water mixture required higher temperature, as expected, since this position is less reactive than the allylic carbon 3. Reduction of the azido group and salt formation as has been previously shown[135] completed the synthesis of oseltamivir phosphate. The researchers mentioned that nitrogen nucleophiles other than azide had been tried to displace the mesylate groups, such as ammonia, benzylamine, allylamine, and *tert*-butylamine, only to provide byproducts **338** and **339** (Figure 14).

Scheme 34. First Synthesis of Oseltamivir Phosphate by Shi's Group

Reagents and conditions: (a) BzCl, TEA, DMAP (cat.), CH$_2$Cl$_2$, 0 °C to rt, 5 h, 98%. (b) HCl (cat.), EtOAc/H$_2$O (4:1), 6 h, 94%. (c) MsCl, TEA, DMAP (cat.), EtOAc, 0 °C, 1 h, 97%. (d) NaN$_3$, DMF/H$_2$O (5:1), - 5 °C to 0 °C, 1.5 h, 95%. (e) (i) Ph$_3$P, THF, rt, 2 h; (ii) TEA, THF/H$_2$O (10:1), rt, overnight, 88%. (f) Ac$_2$O, TEA, EtOAc, 0 °C, 30 min, 98%. (g) 3-Pentanol, BF$_3$•Et$_2$O, -5 to 0 °C, 30 min, 92%. (h) K$_2$CO$_3$, EtOH, rt, 6 h, 90%. (i) MsCl, TEA, CH$_2$Cl$_2$, 0 °C, 1 h, 95%. (j) NaN$_3$, DMF/H$_2$O (5:1), 90 °C, 3 h, 84%. (k) (i) H$_2$ (1 atm), Lindlar catalyst, EtOH, rt, 16 h; (ii) H$_3$PO$_4$, EtOAc/EtOH (1:1), 50 °C, 30 min, 91% (2 steps).

Scheme 35. Optimized Synthesis of Oseltamivir Phosphate by Shi's Group

Reagents and conditions: (a) MsCl, TEA, DMAP (cat.), EtOAc, 0 °C, 1 h, 93%. (b) NaN$_3$, acetone/H$_2$O (5:1), 0 °C, 4 h, 92%. (c) (i) Ph$_3$P, THF, rt, 30 min; (ii) TEA, H$_2$O, rt, 24 h, 84%. (d) Ac$_2$O, TEA, EtOAc, 0 °C, 30 min, 98%. (e) 3-Pentanol, BF$_3$•Et$_2$O, -8 to 0 °C, 1 h, 86%. (f) NaN$_3$, EtOH/H$_2$O (5:1), reflux, 8 h, 88%.
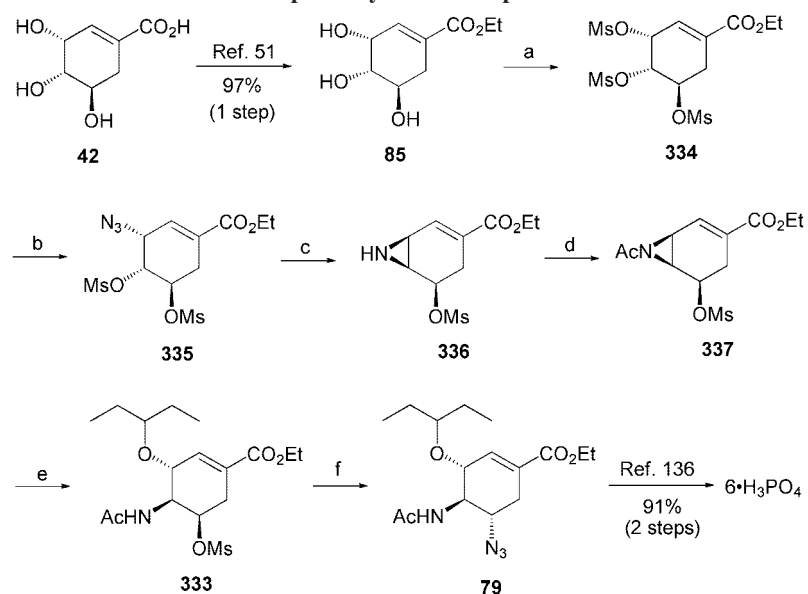
The second synthesis by Shi's group required only nine steps with an outstanding 47% overall yield, which considerably reduced the number of transformations with respect to the first approach and, at the same time, increased the yield by a fair amount. This synthesis is a model of atom-economy, since, for the first time, no protecting groups are needed. The ability to differentiate between the three mesylate groups is key to the success of this approach. The need to resort to azide chemistry on two occasions is more than compensated by the elegance, simplicity, and efficiency of the methodol-

Scheme 36. Synthesis of Oseltamivir by Hayashi's Group

343 (*Syn*, major): 96% ee
344 (*Anti*, minor): 87% ee

Reagents and conditions: (a) 342 (5 mol%), ClCH$_2$CO$_2$H (20 mol%), CH$_2$Cl$_2$, rt, 40 min. (b) (i) 345, Cs$_2$CO$_3$, 0 °C, 3 h, (5*R*)-346/(5*S*)-346: 5:1; (ii) Cs$_2$CO$_3$, EtOH, rt, 15 min.

Reagents and conditions: (c) *p*-Toluenthiol, Cs$_2$CO$_3$, EtOH, -15 °C, 36 h, 70% (from 341; only (5*S*)-349).
(d) TFA, CH$_2$Cl$_2$, 2 h. (e) (i) (COCl)$_2$, DMF (cat.), CH$_2$Cl$_2$, 1 h; (ii) NaN$_3$, H$_2$O/acetone. (f) Ac$_2$O, AcOH, rt, 49 h. (g) Zn, TMSCl, EtOH, 70 °C, 2 h. (h) (i) NH$_3$; (ii) K$_2$CO$_3$, EtOH, 6 h, 82% (5 steps).

ogy. All the steps have been carried out on a gram scale, and this route should become a major player in the goal to develop a scalable process to oseltamivir.

3.19. Synthesis of Oseltamivir *via* Three "One Pot" Operations by Hayashi's Group

Hayashi's group at Tokyo University of Science has published an operationally simple and high yielding approach to oseltamivir.[137] Before embarking on this project, Hayashi established a very specific set of objectives with the goal of developing a synthetic route that allowed for the preparation of large amounts of drug in a short period of time and at low cost. The objectives were as follows: (a) no more than 10 synthetic steps and as few separate operations, such as purifications, as possible; (b) overall yield ≥50%; (c) use of inexpensive reagents exclusively. As a result, the synthetic route shown in Scheme 36 was implemented, which the

authors divided into three "one pot" operations. By "one pot" operation they meant several chemical steps that can be run without workup or any type of purification between steps. A simple solvent evaporation is enough to move forward to the next step. The first of the three "one pot" operations comprises the steps required to prepare intermediate (5*S*)-349 from alkoxyaldehyde 340 and nitroalkene 341; the second one involves the steps required to prepare intermediate 351 from 349; the last one includes the steps to generate oseltamivir (6) from intermediate 351.

As the first stage of the synthesis, the researchers designed a protocol to assemble a highly functionalized ethyl cyclo-hexenecarboxylate core. Thus, aldehyde 340 and nitroalkene 341 underwent an asymmetric Michael reaction in the presence of 5 mol % of diphenylprolinol silyl ether 342[138] as catalyst to give a mixture of nitroaldehydes 343 (*syn*, 96% ee) and 344 (*anti*, 87% ee) stereoisomers in quantitative yield.

Scheme 37. Synthesis of Protected Diol 360 from D-Mannitol by Mandai's Group
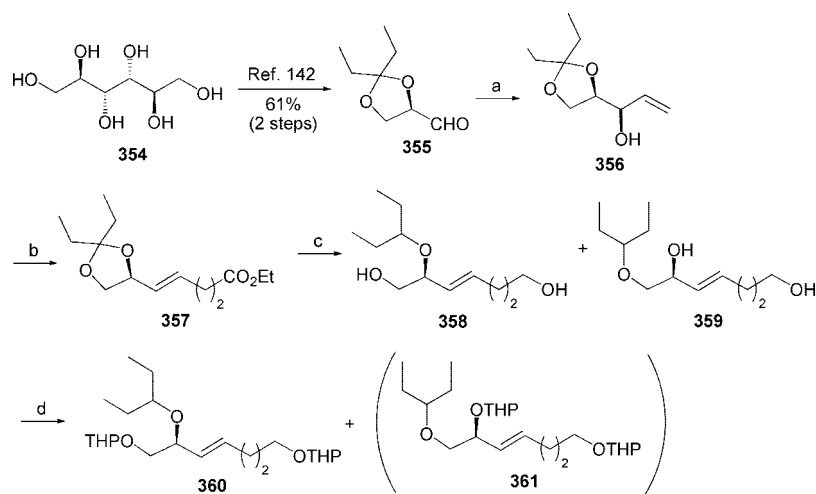
Reagents and conditions: (a) Vinylmagnesium bromide, THF, 0 °C, 1 h, 88%. (b) MeC(OEt)$_3$, 2% EtCO$_2$H, 132 °C, 14 h, 95%. (c) DIBAL-H, toluene, 0 °C, 2 h, then rt, 3 h. (d) 3,4-Dihydro-2H-pyran, PPTS (2 mol%), CH$_2$Cl$_2$, rt, 24 h.
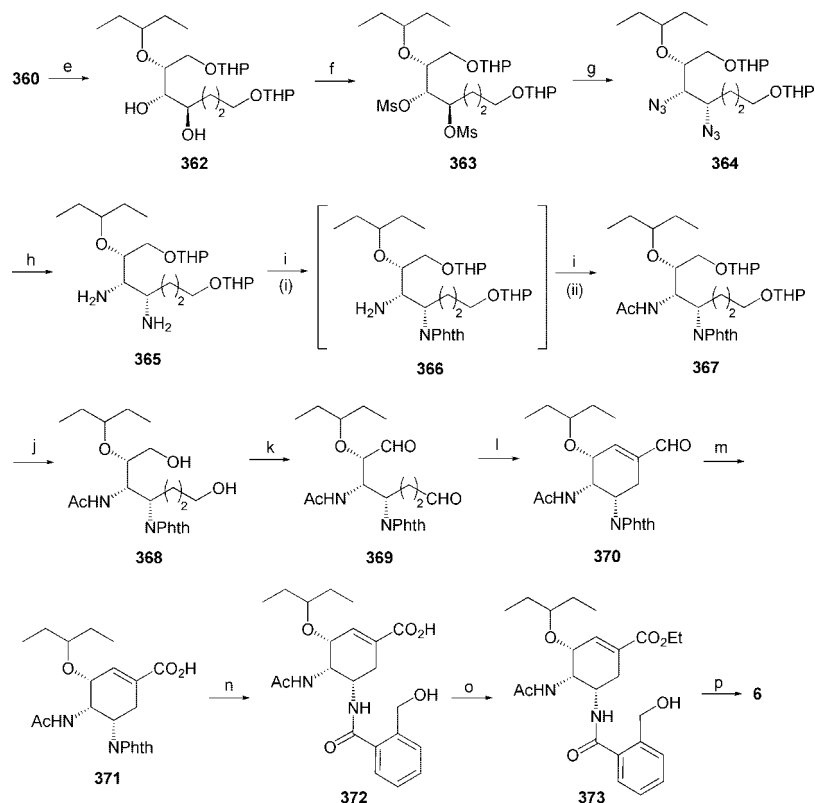
Reagents and conditions: (e) MsNH$_2$, AD-mix-β, $tert$-BuOH/H$_2$O, 0 °C, 8 h, rt, 13 h. (f) MsCl, py, 0 °C, 2 h, then rt, 8 h. (g) NaN$_3$, DMSO, 80 °C, 48 h. (h) LiAlH$_4$, THF, rt, overnight. (i) (i) TEA, DMAP, PhthNCO$_2$Et (0.9 eq each), THF, 0 °C, 1.5 h; (ii) Ac$_2$O, py, rt, 14 h. (j) (i) MeOH, CSA (10 mol%), rt, 1 h; (ii) recrystallization from toluene, 32% from **357**. (k) TEMPO (10 mol%), KBr (20 mol%), aq NaOCl, NaHCO$_3$, CH$_2$Cl$_2$/H$_2$O (2:1), 5 °C, 15 min. (l) Bn$_2$NH•TFA, PhMe, 50 °C, 11 h, 82% (2 steps). (m) NaClO$_2$-NaH$_2$PO$_4$, 2-methyl-2-butene, $tert$-BuOH/THF/H$_2$O (4:1:1), 0 °C, 1 h, then rt, overnight, 86%. (n) NaBH$_4$, i-PrOH/H$_2$O (6;1), rt, overnight, 93%. (o) (i) K$_2$CO$_3$, EtOH/H$_2$O (5:1), rt, 30 min; (ii) solvent removal; (iii) EtI, DMSO, rt, 40 h, 85%. (p) (i) 4 M HCl in dioxane, EtOH, rt, 24 h; (ii) back extraction with NaCO$_3$, 83%.

This *syn/anti* mixture was subjected to a Horner−Wardsworth−Emmons (HWE) reaction with vinylphosphonate **345** to provide a mixture of (5R)- and (5S)-**346** and byproducts **347** and **348**. The formation of hydroxy phosphonate **347** is the result of the *anti* arrangement of its hydroxy and diethoxyphosphoryl groups, which does not lead to elimination, whereas **348** arises from the Michael addition between **345** and **346**. Fortunately, the treatment of the (5R)-**346**/(5S)-**346**/**347**/**348** mixture with Cs$_2$CO$_3$ in ethanol gave exclu-

sively (5R)-**346**/(5S)-**346** as a 5:1 mixture, since compound **347** underwent a retro-aldol followed by a HWE reaction and **348** a retro-Michael reaction. On the other hand, the (5S)-diastereomer had the desired configuration and a protocol had to be developed to prepare it from the major (5R). Even though both acid and base catalysis seemed promising, an alternative, more satisfactory approach was implemented. Thus, the (5R)-**346**/(5S)-**346** mixture was treated with p-toluenethiol and Cs$_2$CO$_3$ in ethanol at −15

Scheme 38. Synthesis of Oseltamivir from L-Methionine Derivative 378 by Mandai's Group

Reagents and conditions: (a) KH, BrCH$_2$CO$_2$H, 60 C, 20 h. (b) SOCl$_2$, 80 °C, 10 h, 94% (2 steps). (c) DIBAL-H, PhMe, -70 °C, 2.5 h, 91%. (d) p-Anisidine, MgSO$_4$, CH$_2$Cl$_2$, 0 °C to rt, overnight, 100%. (e) i-Pr$_2$NEt, **376**, CH$_2$Cl$_2$, -15 °C to rt over 2 h, then rt overnight, 55%, >99% ee. (f) NCS, MeCN/EtOH/H$_2$O, rt, 40 min, 100%. (g) α-Pinene-decalins (1:1), NaHCO$_3$, 155 °C, 6 h, 81%. (h) TFA/CH$_2$Cl$_2$ (3:5), 0 °C to rt, 1.5 h. (i) PhthNCO$_2$Et, TEA, THF, 50 °C, 7.5 h, 86% (2 steps). (j) CAN, MeCN/H$_2$O (1:1), 0 °C, 1 h, 80%. (k) (i) LiHMDS, THF, -78 °C, 15 min; (ii) AcCl, -78 °C, 1 h; (iii) EtSH-TEA, -78 to -20 °C, 3.5 h, 94%. (l) Rh(acac)(CO)$_2$ (5 mol%), BIPHEPHOS (10 mol%), CO/H$_2$ (1:1, 6 atm), THF, 65 °C (autoclave), 7 h, 88%. (m) 10% Pd/C, Et$_3$SiH, CH$_2$Cl$_2$, rt, 1.5 h. (n) Bn$_2$NH·TFA, PhMe, 50 °C, 10 h, 62% (2 steps).

Table 1. Summary of Synthetic Approaches to Zanamivir

source	steps	overall yield (%)	starting material	synthetic route highlights
von Itzsein[14]	5	30	Neu4,5,7,8,9Ac$_5$2en1Me (**10**), prepared from NANA (**1**) in several steps	first disclosure of a neuraminidase inhibitor synthesis; synthesis starts from advanced intermediate; mg- to g-scale; azide chemistry; use of chromatography and lyophilization
Merck Frosst Centre[18]	9	38	NANA (**1**)	high-yielding process; mg-scale; azide chemistry; first application of Mitsunobu reaction to glycals; freeze-drying and multiple chromatographies; pressure vessel step.
Glaxo[28]	9	8.3	NANA(**1**)	multi-g scale; most intermediates isolated via recrystallization; desalting and ion-exchange chromatography employed; azide chemistry run on 600-g scale.
Yao[29]	24	0.25	D-glucono-δ-lactone (**26**)	cheap starting material; cyclohexene ring built from acyclic intermediates; very long synthesis; very low overall yield; multiple chromatographies; mg-scale; azide chemistry

°C to provide intermediate (5S)-**349** as the only diastereomer, which could be purified by chromatography (Scheme 36 (bottom)). Under the basic reaction conditions, the (5R)-diastereomer reacts with p-toluenethiol and it then undergoes isomerization at the carbon 5 position to provide the more stable (5S)-**349**.

With the ethyl cyclohexenecarboxylate core in hand, the synthesis continued with the cleavage of the *tert*-butyl ester in the presence of TFA to provide crude acid **350**, which

was first converted to the corresponding acid chloride with oxalyl chloride, followed by the reaction with NaN$_3$ to generate acyl azide **351**. The authors highlighted the fact that this intermediate is pure enough to be used in the next step without any additional purification. The reaction of azide **351** with Ac$_2$O in acetic acid at room temperature triggered a Curtius rearrangement under very mild conditions and subsequent amide bond formation to give acetamide **352**.[139] The fact that the Curtius rearrangement proceeds without
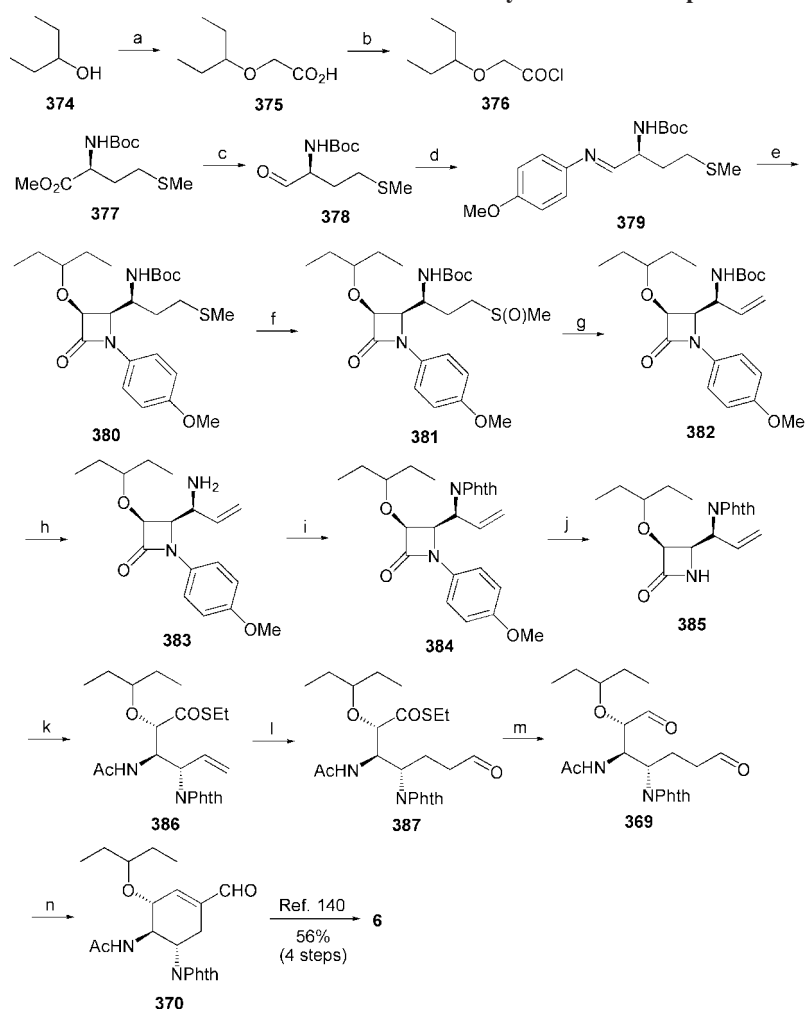
Table 2. Summary of Synthetic Approaches to Oseltamivir

source	steps	overall yield (%)	starting material	synthetic route highlights
Gilead[39]	14	15	(−)-shikimic acid (**42**)	synthesis of acid candidate **56**; mg-scale; azide chemistry
Gilead[39]	6	40	(−)-quinic acid (**57**)	synthesis of epoxide **43**; g-scale
Gilead[43]	12	4.4	(−)-quinic acid (**57**)	multi-kg scale; only 3 isolated crystalline intermediates; no chromatography; azide chemistry; minimal protecting group manipulations
F. Hoffmann-La Roche Ltd.[51]	8	35	(−)-quinic acid (**57**)	synthesis of epoxide **74**; kg-scale; overall yield doubled; 30% reduction in number of operations
F. Hoffmann-La Roche Ltd.[51]	4	66	(−)-shikimic acid (**42**)	synthesis of ketal **70**; kg-scale; production time reduced by 50% to epoxide **74**; higher cost than route from (−)-quinic acid (**57**)
F. Hoffmann-La Roche Ltd.[54]	6	35	epoxide **74**	multi-g scale; azide-free; allyl amine as nitrogen nucleophile; chromatography-free
Roche Colorado Corporation[59]	8	61	epoxide **74**	multi-g scale; azide-free; high-yielding; allylamine and *tert*-butylamine as nitrogen nucleophiles
F. Hoffmann-La Roche Ltd.[36]	9	3.2	furan (**105**) and ethyl acrylate (**106**)	Diels−Alder approach; synthesis of intermediate **116** from inexpensive starting materials; azide chemistry; minimal protecting group manipulations
F. Hoffmann-La Roche Ltd.[36]	14	28	1,6-dimethoxyphenol (**117**) and mesylate **118**	desymmetrization approach; inexpensive starting materials; azide chemistry
Corey[64]	11	27	1,3-butadiene (**133**) and 2,2,2-trifluoroethyl acrylate (**134**)	mg-scale; high ee Diels−Alder; high overall yield; azide-free; unusual approach to introduce amino functionalities
Okamura[67]	7	11	*N*-nosyl-3-hydroxy-2-pyridone (**145**) and ethyl acrylate (**146**)	synthesis of racemic Corey's intermediate **142**; low yield; mg-scale; chiral resolution necessary; additional steps to prepare starting material **145**
Shibasaki[72]	17	1.4	*N*-3,5-dinitrobenzoylaziridine **155**	mg-scale; azide chemistry; chirality introduced early in the synthesis; low catalyst loading; SeO$_2$ and DMP oxidations; Mitsunobu chemistry; extensive protecting group manipulation
Shibasaki[73]	20	16	*N*-3,5-dinitrobenzoylaziridine **155**	mg-scale; high yield; DMP oxidation; extensive protecting group manipulation; azide chemistry
Shibasaki[73]	12	7.4	azide **158**	mg-scale; sealed tube reaction; two Mitsunobu reactions; azide chemistry; several protecting group manipulations
Shibasaki[74]	14	2.8	1-(trimethylsiloxy)-1,3-butadiene (**199**) and fumaryl chloride (**200**)	commercially available starting materials; very low overall yield; chiral HPLC for resolution of intermediate; minimal protecting group manipulation; Curtius rearrangement at high temp; Mitsunobu chemistry
Shibasaki[75]	12	16	1-(trimethylsiloxy)-1,3-butadiene (**199**) and dimethyl fumarate (**210**)	commercially available starting materials; introduction of chirality in first step; low catalyst loading; scalable asymmetric Diels−Alder reaction; azide chemistry; high temp Curtius rearrangement; Mitsunobu chemistry; minimal protecting group manipulation
Yao[93]	25	8	L-serine (**229**)	inexpensive, commercially available starting material; very long synthesis; mg-scale; excellent overall yield; unusual approach for building cyclohexene ring; extensive protecting group manipulation; multiple chromatographies; azide-free
Fukuyama[101]	14	5.6	pyridine (**255**)	inexpensive starting material; azide-free; extensive protecting group manipulation; chirality introduced early in the synthesis
Fang[108]	16	14	D-xylose	inexpensive, commercially available starting material; mg-scale; high yield; azide chemistry; extensive protecting group manipulation; multiple chromatographies; novel approaches for the introduction of functionality
Fang[111]	11	26	*cis*-1,2-dihydrodiol **285**	chemoenzymatic synthesis; g-scale; azide chemistry; short and very high-yielding synthesis; crystalline intermediates
Fang[111]	11	22	*cis*-1,2-dihydrodiol **285**	chemoenzymatic synthesis; g-scale; very high yield; azide-free synthesis
Kann[118]	14	5	cyclohexadienoic acid ethyl ester **297**	low-yielding; unusual approach; easily adapted for analogue preparation; HPLC separation of diastereomers; azide chemistry; scalability uncertain
Trost[127]	8	30	lactone **309**	shortest synthesis to date; commercially available starting material; high yield and ee; azide-free; use of MW and hydrazine; cost of goods may be an issue on scale; no information on scale
Banwell[132]	13	6.2	*cis*-1,2-dihydrodiol **285**	chemoenzymatic synthesis; azide-free; less practical than similar route by Fang[111]
Shi[135]	13	40	(−)-shikimic acid (**42**)	mg-scale; very high yield; azide chemistry; minimal protecting group manipulation; very efficient aziridine-opening step; extensive use of chromatography
Shi[136]	9	47	(−)-shikimic acid (**42**)	g-scale; very high yield; short process; no protecting group chemistry; azide chemistry; simple transformations; atom-economic
Hayashi[137]	9	57	aldehyde **336** and nitroalkene **337**	synthesis of free base of oseltamivir; additional steps for starting material preparation; highest yield to date; operationally simple; minimal intermediate purification; azide chemistry; no information on scale
Mandai[140]	18	7.5	D-mannitol	synthesis of free base of oseltamivir; no chromatography; azide chemistry at high temp; extensive protecting group manipulation; novel approach to cyclohexene ring; no information on scale
Mandai[141]	18	8 (from **380**)	L-methionine derivative **380**	azide-free; simplified protecting group manipulation compared to D-mannitol route; no information on scale

heating decreases the risks associated with the handling of potentially explosive acyl azides. The nitro group in **352** was reduced with Zn metal under acidic conditions to produce amine **353**. After ammonia had been bubbled through the mixture to form a Zn^{II}−NH$_3$ complex, the addition of K$_2$CO$_3$ caused the elimination of *p*-toluenethiol to give oseltamivir in excellent yield after purification by acid/base extraction.

This 9-step approach (10 steps to the phosphate salt) characterizes by its operational simplicity, since only one intermediate purification is required ((5*S*)-**349**, chromatography) and for excellent overall yield (57%), which should make it amenable for scale-up. Additional steps are expected to prepare the two starting materials, aldehyde **340** and

nitroalkene **341**, which should bring the overall yield down. Some interesting features of this process are the use of inexpensive reagents, relatively nontoxic metals such as Na, K, Cs, and Zn, and the possibility of running this chemistry under nonanhydrous conditions.

3.20. Synthetic Approaches to Oseltamivir by Mandai's Group

Mandai's group at the Kurashiki University of Science & the Arts in Japan has published two syntheses of oseltamivir from readily available and inexpensive materials. The first approach starts from D-mannitol and builds the cyclohexene

ring from an acyclic intermediate *via* an intramolecular aldol condensation of dialdehyde **372**.[140] The second methodology starts from L-methionine and accesses this same dialdehyde *via* the ring-opening of *cis*-β-lactam intermediate **388**.[141]

3.20.1. Synthesis of Oseltamivir from D-Mannitol

The preparation of oseltamivir from D-mannitol (**354**) is shown in Scheme 37.[140] Thus, this material was converted into protected aldehyde **355** by a reported procedure[142] and has the advantage that it conveniently introduces the 3-pentyl group without resorting to the usual BF$_3$·Et$_2$O-catalyzed ring-opening of an aziridine intermediate. This aldehyde was then treated with vinylmagnesium bromide in THF to produce a mixture of diastereomeric alcohols that, after orthoester Claisen rearrangement in the presence of triethyl orthoacetate and a catalytic amount of propionic acid, generated ester **357** as a colorless oil in very high yield after distillation. The acetal and the ester functionalities were simultaneous cleaved with DIBAL-H[143] to provide a mixture of regioisomers **358** (desired) and **359** in a 10:1 ratio. Since this mixture could not be separated, it was carried over to the next step and treated with 3,4-dihydro-2*H*-pyran to give THP-protected diol **360**. The authors did not mention whether regioisomer **361** was also obtained.

With **360** in hand, the stage was set for the asymmetric dihydroxylation of the alkene functionality with AD-mix-β,[144] which gave diol **362** as the only product (Scheme 37 (bottom). This intermediate was converted to the corresponding dimesylate **363** under standard conditions, and the mesylate groups were displaced with NaN$_3$ in hot DMSO to afford diazide **364**. The azido groups were reduced with LAH to diamino intermediate **365**. The researchers pointed out the fact that when this reduction was attempted with H$_2$ and 10% Pd/C, the reaction was not reproducible, most likely due to catalyst poisoning by the impurities present. The less hindered amino group was regioselectively protected with *N*-ethoxycarbonylphthalimide to produce intermediate **366**, which, without isolation, was treated with Ac$_2$O to acetylate the remaining amino group and afford acetamide **367**. The THP-protecting groups could be removed with 10-camphorsulfonic acid, and the resulting diol **368** was isolated from toluene. A TEMPO[145] oxidation of **368** provided dialdehyde **369**, and this substrate was subjected to an intramolecular aldol condensation with Bn$_2$NH·TFA as base[146] to generate cyclic aldehyde **370**. This transformation proceeded very smoothly, and no elimination or aromatization products were identified. The aldehyde was oxidized to the corresponding acid with NaClO$_2$,[99] and with the goal of avoiding a chromatographic purification of the rest of intermediates, the phthalimide moiety was first reduced with NaBH$_4$[147] in IPA/water to provide amide **372** and the acid was then esterified with EtI to generate **373**. Oseltamivir was finally isolated after cleavage of the amide bond with HCl in dioxane.

This synthesis required 18 steps and provided the free base of oseltamivir in 7.5% overall yield. Remarkably, no chromatographic purification of any of the intermediates was required, which is a strong point in its favor to become a good candidate for large scale production. A new approach for synthesizing the cyclohexene ring is provided *via* an intramolecular aldol condensation that proceeded very cleanly. Some of the caveats of the synthesis are the need for several protecting groups and azide chemistry at high temperature (80 °C in DMSO). No information was provided in the publication on the scale at which this chemistry was carried

out, but many of the steps are transformations well precedented in the literature, such as the preparation of aldehyde **355**, the DHP-protection, and the TEMPO and NaClO$_2$ oxidations, and should be, in principle, adaptable to large scale.

3.20.2. Synthesis of Oseltamivir from L-Methionine

The second approach to oseltamivir by this same group relies on naturally occurring L-methionine as a handle to introduce the chirality on the ring.[141] The synthesis started with the reaction between 3-pentanol (**374**) a bromoacetic acid[148] to provide acid **375**, which was converted to the corresponding acid chloride **376** in the presence of SOCl$_2$.

The preparation of imine **379** as the other coupling partner was carried out by reducing methyl ester **377**, derived from L-methionine, with DIBAL-H at cryogenic temperature to provide aldehyde **378**. The reaction of **378** with *p*-anisidine and MgSO$_4$ as dehydrating agent afforded imine **379** in quantitative yield. β-Lactam **380** was then generated *via* a Staudinger reaction[149] between **376** and **379** in excellent ee (>99%) and fair yield. The oxidation of the sulfide functionality and thermal elimination provided alkene **382**,[150] whose Boc-protecting group was replaced by a phthaloyl group to provide intermediate **384**, which possessed better stability toward acidic conditions. The *p*-methoxyphenyl group was removed through CAN oxidation[151] to give lactam **385** without affecting the phthaloyl protecting group. The lactam ring was opened in one pot by first acetylating the nitrogen on the ring with AcCl followed by reaction with EtSH·TEA to generate thiol ester **386**, which underwent a hydroformylation reaction[152] with Rh(acac)(CO)$_2$ as catalyst and ligand BIPHEPHOS (**395**, Figure 15)[153] to afford
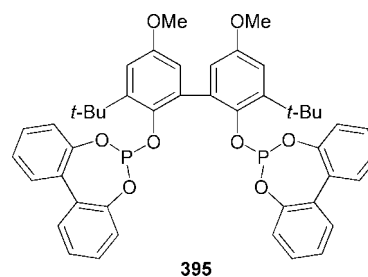
Figure 15. Structure of hydroformylation ligand BIPHEPHOS.

aldehyde **387**. The ratio of linear (**387**) to branched byproduct was >30:1. The thiol ester was reduced with Et$_3$SiH and 10% Pd/C to provide dialdehyde **369**, which underwent an intramolecular aldol reaction as in the preceding synthesis from D-mannitol to afford cyclic aldehyde **370**. The completion of the synthesis of oseltamivir was carried out as has been shown in the preceding route by the same group.[140]

This second route by Mandai's group consisted of 18 steps and gave the free base of oseltamivir in 8% yield from L-methionine derivative **377**, whose preparation from the amino acid would require additional steps. The researchers managed to find an alternative azide-free route and exploited the versatility of β-lactams as chiral building blocks to produce material in very high ee. The protecting group chemistry has been simplified with respect to the D-mannitol approach, but unfortunately, this did not translate into a shorter process. The probable lower cost of goods of the D-mannitol route is an additional consideration in its favor, but neither route seems to have a clear advantage over the other.

4. Summary of Synthetic Approaches to Zanamivir and Oseltamivir

Tables 1 and 2 summarize the synthetic routes to zanamivir and oseltamivir published to date respectively.[154] Special attention has been paid to factors such as scale, the use of inexpensive and readily available starting materials, the need for protecting groups, purification techniques, and whether or not the route employs azide as nitrogen nucleophile. Additional comments have been included to highlight other aspects of the syntheses that have been considered relevant.

5. Conclusions

As was mentioned at the beginning of this review, zanamivir and oseltamivir are the only two drugs approved to combat both influenza A and B. Zanamivir has seen limited use in patients not only due to its low bioavailability and the need to administer it topically to the respiratory tract by intranasal spray or by inhalation but also, according to its discoverer Biota, because of the lack of support to adequately promote and market the drug by its partner GlaxoSmithKline.[155] As a result, only one synthesis of zanamivir (Yao,[29] 2004) has been reported since Glaxo's large scale preparation in 1995.[28] Therefore, oseltamivir is essentially the only weapon currently available to treat the disease and the research efforts of the scientific community have almost exclusively focused on the development of new approaches to this drug.

After reviewing the current status of oseltamivir synthesis, several goals can be identified to develop practical routes that can be converted into commercial processes:
(1) Reduce the number of steps and operations to increase throughput and overall yield: the synthetic routes described in this review range anywhere from 8 to 25 steps. Gilead[43] was able to produce multi-kilogram quantities of oseltamivir in 14 steps, but syntheses shorter than 10 steps have already been reported by Trost,[127] Shi,[136] and Hayashi.[137]
(2) Reduce the use of protecting groups: it is imperative that the use of protecting group chemistry is minimized so that throughput can be increased. In a highly functionalized molecule such as oseltamivir this is a difficult task, but the syntheses by Gilead,[43] F. Hoffmann-La Roche Ltd.,[36] Shibasaki,[74,75] and, especially, Shi[136] serve to prove that it is feasible to accomplish this objective.
(3) Employ nitrogen nucleophiles other than azide: even though the use of azide is widespread among the processes that have been described, many groups have been able to find alternatives for the introduction of the amino and acetamido groups on the ring, such as F. Hoffmann-La Roche Ltd.,[54] Roche Colorado Corporation,[59] Corey,[64] Yao,[93] Fukuyama,[101] Fang,[111] Trost,[127] Banwell,[132] and Mandai.[141]
(4) Employ a low cost of goods: it seems clear that, for many of the groups that have reported approaches to oseltamivir, it is very important to start from inexpensive and readily available starting materials, especially if they already possess some of the chirality that is found in the target molecule or if that chirality can be used as a handle to introduce the desired stereochemistry. The protocols developed by F. Hoffmann-La Roche Ltd.,[36] Yao,[93] Fukuyama,[101] Fang,[108,111] Banwell,[132] and Mandai[140,141] are examples of this.
(5) Develop a convergent synthesis: all syntheses of oseltamivir to date are linear. A major breakthrough would be the development of a convergent synthesis that could bring together two fragments with some or all the functionality

already present, with the goal of decreasing the number of steps of the longest synthetic branch. A Diels−Alder reaction seems an obvious choice to build the cyclohexene ring, but the densely functionalized oseltamivir molecule may make this approach unfeasible.

Some of the syntheses described above meet several of these criteria to be considered for large scale production, such as the examples by Fang,[111] Trost,[127] Shi,[136] and Hayashi.[137] The "greenness" of the route is another factor to take into consideration, and this has been recently reviewed for six industrial syntheses and nine approaches by academic groups to oseltamivir using an algorithm to determine their global material efficiency performance.[156]

There are concerns that it is unavoidable that a pandemic will occur within the next few years,[157,158] with its origin most likely in Asia, and that it can reach the United States in only 3 months. Even though a vaccine for chickens against the H5N1 strain (the virus now causing avian flu) already exists and a human version program is underway, the need for up to six months to produce the vaccine may render it useless. In addition, there is fear that if a vaccine is widely used, the virus will mutate, thus rendering it ineffective. Therefore, continuous efforts are needed to develop drugs which are safe and effective as well as to devise new methods of drug delivery that can maintain the drug level in the lung for longer periods of time without any side effects.

The information presented in this review shows that the synthesis of neuraminidase inhibitors, and oseltamivir in particular, is a very active field of research. Even though both zanamivir and oseltamivir are currently available for the treatment of influenza, the fear of a devastating pandemic and the possibility that drug-resistant strains of avian flu can emerge as a result of these treatments[159] has spurred the imagination of synthetic organic chemists, both in academia and industry, to produce new structures that can combat the disease. As a consequence, a large number of publications on the syntheses of new neuraminidase inhibitors has been generated in recent years.[160] The current manufacturing process for oseltamivir guarantees the availability of large amounts of the drug, and many nations have drawn up pandemic-preparedness plans[161] and stockpiled millions of doses to be used strategically should a widespread influenza outbreak occur.[162] On the other hand, the limited availability of (−)-shikimic acid and (−)-quinic acid in nature is a major drawback for the current industrial manufacturing, and new synthetic approaches that begin from more readily available and inexpensive starting materials are indispensable.

Many of the routes presented in this review show amazing ingenuity in their strategies to assemble the molecule but are lengthy in their present state and rely heavily on protecting groups to accomplish their goal, which makes them impractical for manufacturing scale. But, at the same time, their mere existence is a sign of the imagination displayed by synthetic organic chemists to confront difficult problems and guarantees that, eventually, alternative and practical paths to these important drugs and new ones will be available.[163]

6. Abbreviations

acac	acetylacetonate
AIBN	2,2′-azobis(2-methylpropionitrile)
CAN	cerium(IV) ammonium nitrate
CBz	benzyloxycarbonyl
CDI	1,1′-carbonyldiimidazole

COD	cyclooctadiene
CSA	(1*S*)-(+)-10-camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DEAD	diethyl azodicarboxylate
DHP	3,4-dihydro-2*H*-pyran
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DIPEA	diisopropylethyl amine
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMP	Dess−Martin periodinane
DMSO	dimethylsulfoxide
DPPA	diphenylphosphoryl azide
Dppf	bis(diphenylphosphino)ferrocene
EDCl	*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride
HOBt	1-hydroxybenzotriazole
IPA	2-propanol
KHMDS	potassium hexamethyldisilazide
m-CPBA	*m*-chloroperbenzoic acid
MOM	methoxymethyl
MsCl	methanesulfonyl chloride
MTBE	*tert*-butyl methyl ether
MW	microwave
NaHMDS	sodium hexamethyldisilazide
NANA	*N*-acetylneuraminic acid
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMO	4-methylmorpholine *N*-oxide
NMP	1-methyl-2-pyrrolidinone
PDC	pyridinium dichromate
PLE	pig liver esterase
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
PPTS	pyridine *p*-toluenesulfonate
Py	pyridine
rt	room temperature
SES	2-(trimethylsilyl)ethanesulfonyl
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TEA	triethylamine
TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
THP	tetrahydropyran
TMS	trimethylsilyl
Tr	trityl
p-TsCl	*p*-toluenesulfonyl chloride
p-TsOH	*p*-toluensulfonic acid

7. References

(1) (a) Service, R. F. *Science* **1997**, *275*, 756. (b) Giezen, W. P. *Epidemiol. Rev.* **1982**, *4*, 25. (c) Nicholson, K. G. *Epidemiol. Infect.* **1996**, *116*, 51. (d) Fischetti, M. *Sci. Am.* **2001**, *284*, 82.

(2) (a) Laver, W. G.; Bischofberger, N.; Webster, R. G. *Sci. Am.* **1999**, *280*, 78. (b) Laver, W. G.; Bischofberger, N.; Webster, R. G. *Perspect. Biol. Med.* **2000**, *43*, 173.

(3) Centers for Disease Control and Prevention. Prevention and control of influenza. MMWR Morbid Mortal Wkly Rep. 2000, *49* (RR-3), 1.

(4) (a) Meanwell, N. A.; Krystal, M. *Drug Discov. Today* **1996**, *1*, 316. (b) Meanwell, N. A.; Krystal, M. *Drug Discov. Today* **1996**, *1*, 388. (c) Schmidt, A. C. *Drugs* **2004**, *64*, 2031.

(5) (a) Hay, A. J.; Wolstenholme, A. J.; Skehel, J. J.; Smith, M. H. *EMBO J.* **1985**, *4*, 3021. (b) Hay, A. J. *Semin. Virol.* **1992**, *3*, 21.

(6) Palese, P.; Tobita, K.; Ueda, M.; Compans, R. W. *Virology* **1974**, *61*, 397.

(7) Hayden, F. G.; Minocha, A.; Spyder, D. A. *Antimicrob. Agents Chemother.* **1985**, *28*, 216.

(8) (a) Hayden, F. G.; Couch, R. B. *Rev. Med. Virol.* **1992**, *2*, 89. (b) Hayden, F. G.; Belshe, R. B.; Clover, R. D.; Hay, A. J.; Oakes, M. G.; Soo, W. *N. Engl. J. Med.* **1989**, *321*, 1696. (c) Grambas, S.; Bennett, M. S.; Hay, A. J. *Virology* **1992**, *191*, 541.

(9) (a) Meindl, P.; Bodo, G.; Palese, P.; Schulman, J.; Tuppy, H. *Virology* **1974**, *58*, 457. (b) Palese, P.; Compans, R. W. *J. Gen. Virol.* **1976**, *33*, 139. (c) Palese, P.; Schulman, J. L.; Bodo, G.; Meindl, P. *Virology* **1974**, *59*, 490.

(10) (a) Varghese, J. N.; Laver, W. G.; Colman, P. M. *Nature* **1983**, *303*, 35. (b) Colman, P. M.; Varghese, J. N.; Laver, W. G. *Nature* **1983**, *303*, 41.

(11) (a) Bethell, R.; Smith, P. *Drugs Fut.* **1998**, *23*, 1099. (b) Abdel-Magid, A. F.; Maryanoff, C. A.; Mehrman, S. J. *Curr. Opin. Drug Discovery Dev.* **2001**, *4*, 776. (c) Wang, G. T. *Expert Opin. Ther. Patents* **2002**, *12*, 845. (d) Hochgürtel, M.; Kroth, H.; Piecha, D.; Hofmann, M. W.; Nicolau, C.; Krause, S.; Schaaf, O.; Sonnenmoser, G.; Eliseev, A. V. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 3382. (e) Chand, P. *Expert Opin. Ther. Patents* **2005**, *15*, 1009. (f) Johnson, D. S.; Li, J. J. In *The Art of Drug Synthesis*; Johnson, D. S., Li, J. J., Eds.; John Wiley & Sons: New York, 2007.

(12) von Itzstein, M.; Wu, W.-Y.; Kok, G. B.; Pegg, M. S.; Dyason, J. C.; Jin, B.; Phan, T. V.; Smythe, M. L.; White, H. F.; Woods, J. M.; Bethell, R. C.; Hotham, V. J.; Cameron, J. M.; Penn, C. R. *Nature* **1993**, *363*, 418.

(13) (a) Chapple, K. J.; Hendrick, A. E.; McCarthy, M. W. *Ann. Pharmacother.* **2000**, *34*, 798. (b) Fleming, D. M. *Expert Opin. Pharmacother.* **2003**, *4*, 799. (c) McNicholl, R.; McNicholl, J. J. *Ann. Pharmacother.* **2001**, *35*, 57.

(14) von Itzstein, M.; Wu, W.-Y.; Jin, B. *Carbohydr. Res.* **1994**, *259*, 301.

(15) von Itzstein, M.; Jin, B.; Wu, W.-Y.; Chandler, M. *Carbohydr. Res.* **1993**, *244*, 181.

(16) Schreiner, E.; Zbiral, E.; Kleineidam, R. G.; Schauer, R. *Liebigs. Ann. Chem.* **1991**, 129.

(17) Kim, Y.; Lin, Y.-T.; Mosher, H. S. *Tetrahedron Lett.* **1988**, *29*, 3183.

(18) Scheigetz, J.; Zamboni, R.; Bernstein, M. A.; Roy, B. *Org. Prep. Proc. Int.* **1995**, *27*, 637.

(19) Colman, P. M.; von Itzstein, L. M.; Varghese, J. N.; Wu, W.-Y.; Phan, T. V.; White, H. F. PCT Int. Appl. WO92/06691 A1 (1992); Chem. Abstr. 1992, *117*, 131501.

(20) Warner, T. G.; O'Brien, J. S. *Biochemistry* **1979**, *18*, 2783.

(21) Kuhn, R.; Luetz, P.; Macdonald, D. L. *Chem. Ber.* **1966**, *99*, 611.

(22) Okamoto, K.; Kondo, T.; Goto, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 631.

(23) von Itzstein, L. M.; Wu, W.-Y.; Phan, T. V.; Danylec, B.; Jin, B. PCT Int. Appl. WO91/16230 A1 (1991); Chem. Abstr. 1992, *117*, 49151.

(24) Thompson, A. S.; Humphrey, G. R.; DeMarco, A. M.; Mathre, D. J.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 5886.

(25) Bannard, R. A. B.; Casselman, A. A.; Cockburn, W. F.; Brown, G. M. *Can. J. Chem.* **1958**, *36*, 1541.

(26) Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *J. Org. Chem.* **1992**, *57*, 2497.

(27) Dharmpal, S. D.; Kozikowski, A. P. *Tetrahedron Lett.* **1994**, *35*, 977.

(28) Chandler, M.; Bamford, M. J.; Conroy, R.; Lamont, B.; Patel, B.; Patel, V. K.; Steeples, I. P.; Storer, R.; Weir, N. G.; Wright, M.; Williamson, C. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1173.

(29) Liu, K.-G.; Yan, S.; Wu, Y.-L.; Yao, Z.-J. *Org. Lett.* **2004**, *6*, 2269.

(30) Liu, K.-G.; Zhou, H.-B.; Wu, Y.-L.; Yao, Z.-J. *J. Org. Chem.* **2003**, *68*, 9528.

(31) Yadav, J. S.; Reddy, B. V. S.; Rao, K. V.; Raj, K. S.; Prasad, A. R. *Synthesis* **2002**, 1061.

(32) Ikunaka, M.; Matsumoto, J.; Nishimoto, Y. *Tetrahedron: Asymmetry* **2002**, *13*, 1201.

(33) Liu, K.-G.; Yan, S.; Wu, Y.-L.; Yao, Z.-J. *J. Org. Chem.* **2002**, *67*, 6758.

(34) Marra, A.; Sinay, P. *Carbohydr. Res.* **1989**, *190*, 317.

(35) Gregar, T. Q.; Gervay-Hague, J. *J. Org. Chem.* **2004**, *69*, 1001.

(36) Abrecht, S.; Harrington, P.; Iding, H.; Karpf, M.; Trussardi, R.; Wirz, B.; Zutter, U. *Chimia* **2004**, *58*, 621.

(37) Graul, A.; Leeson, P. A.; Castañer, J. *Drugs Fut.* **1999**, *24*, 1189.

(38) (a) Behera, M. *Chemtracts* **2006**, *19*, 38. (b) Farina, V.; Brown, J. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 7330. (c) Abrecht, S.; Federspiel, M. C.; Estermann, H.; Fischer, R.; Karpf, M.; Mair, H.-J.; Oberhauser, T.; Rimmler, G.; Trussardi, R.; Zutter, U. *Chimia* **2007**, *61*, 93. (d) Shibasaki, M.; Kanai, M. *Eur. J. Org. Chem.* **2008**, 1839. (e) Gong, J.; Xu, W. *Curr. Med. Chem.* **2008**, *15*, 3145.

(39) Kim, C. U.; Lew, W.; Williams, M. A.; Liu, H.; Zhang, L.; Swaminathan, S.; Bischofberger, N.; Chen, M. S.; Mendel, D. B.; Tai, C. Y.; Laver, W. G.; Stevens, R. C. *J. Am. Chem. Soc.* **1997**, *119*, 681.

(40) McGowan, D. A.; Berchtold, G. A. *J. Org. Chem.* **1981**, *46*, 2381.

(41) (a) Shing, T. K. M.; Tang, Y. *Tetrahedron* **1990**, *46*, 6575. (b) Molin, H.; Pring, B. G. *Tetrahedron Lett.* **1985**, *26*, 677. (c) Wan, X.; Doridot, G.; Joullié, M. M. *Org. Lett.* **2007**, *9*, 977.

(42) Ulibarri, G.; Nadler, W.; Skrydtrup, T.; Audrian, H.; Chiaroni, A.; Riche, C.; Grierson, D. S. *J. Org. Chem.* **1995**, *60*, 2753.

(43) Rohloff, J. C.; Kent, K. M.; Postich, M. J.; Becker, M. W.; Chapman, H. H.; Kelly, D. E.; Lew, W.; Louie, M. S.; McGee, L. R.; Prisbe, E. J.; Schultze, L. M.; Yu, R. H.; Zhang, L. *J. Org. Chem.* **1998**, *63*, 4545.

(44) Cleophax, J.; Leboul, J.; Mercier, D.; Gaudemer, A.; Gero, S. D. *Bull. Soc. Chim. Fr.* **1973**, *11*, 2992.

(45) (a) Trost, B. M.; Kelnan, E. *J. Am. Chem. Soc.* **1978**, *100*, 7779. (b) Genet, J. P.; Balabane, M.; Backvall, J. E.; Nystrom, J. E. *Tetrahedron Lett.* **1983**, *24*, 2745.

(46) (a) Lewbart, M. L.; Scheneider, J. J. *J. Org. Chem.* **1969**, *34*, 3505. (b) Zderic, J. A.; Moffatt, J. G.; Kau, D.; Gerzon, K.; Fitzgibbon, W. E. *J. Med. Chem.* **1965**, *8*, 275.

(47) Hunter, R.; Bartels, B. *J. Org. Chem.* **1993**, *58*, 6756.

(48) Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353, and refs 276−282 cited therein.

(49) Prisbe, E. J.; Verheyden, J. P. H.; Montgomery, W. W.; Strosberg, A. M. *J. Med. Chem.* **1986**, *29*, 239.

(50) Knapp, S.; Shieh, W.-C.; Jaramillo, C.; Trilles, R. V.; Nanden, S. R. *J. Org. Chem.* **1994**, *59*, 946.

(51) Federspiel, M.; Fischer, R.; Hennig, M.; Mair, H.-J.; Oberhauser, T.; Rimmler, G.; Albiez, T.; Bruhin, J.; Estermann, H.; Gandert, C.; Göckel, V.; Götzö, S.; Hoffmann, U.; Huber, G.; Janatsch, G.; Lauper, S.; Röckel-Stäbler, O.; Trussardi, R.; Zwahlen, A. G. *Org. Process Res. Dev.* **1999**, *3*, 266.

(52) Mair, H.-J. EP 957078 A1, 1999; Chem. Abstr. 1999, *131*, 336883.

(53) (a) Srikrishna, A.; Viswajanani, R. *Tetrahedron* **1995**, *51*, 3339. (b) Mori, A.; Ishihara, K.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*, 987. (c) Ishihara, K.; Mori, A.; Yamamoto, H. *Tetrahedron Lett.* **1987**, *28*, 6613. (d) Gesson, J. P.; Jacquesy, J. C.; Mondon, M. *Tetrahedron Lett.* **1989**, *30*, 6503. (e) Kotsuki, H.; Nishikawa, H.; Mori, Y.; Ochi, M. *J. Org. Chem.* **1992**, *57*, 5036. (f) Homma, K.; Mukaiyama, T. *Heterocycles* **1990**, *31*, 443. (g) Robl, J. A.; Cimarusti, M. P.; Simpkins, L. M.; Weller, H. N.; Pan, Y. Y.; Malley, M.; DiMarco, J. D. *J. Am. Chem. Soc.* **1994**, *116*, 2348. (h) Burgess, L. E.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 1656. (i) Meyers, A. I.; Tschantz, M. A.; Brengel, G. P. *J. Org. Chem.* **1995**, *60*, 4359.

(54) Karpf, M.; Trussardi, R. *J. Org. Chem.* **2001**, *66*, 2044.

(55) Chini, M.; Crotti, P.; Favero, L.; Macchia, F.; Pineschi, M. *Tetrahedron Lett.* **1994**, *35*, 433.

(56) Afarinkia, K.; Cadogan, J. I. G.; Rees, C. W. *Synlett* **1990**, *7*, 415.

(57) De Kimpe, N.; De Smaele, D.; Sakonyi, Z. *J. Org. Chem.* **1997**, *62*, 2448.

(58) Oliya, R.; Yuan, L.-C.; Dahl, T. C.; Swaminathan, S.; Wang, K.-Y.; Lee, W. A. *Pharm. Res.* **1998**, *15*, 1300.

(59) Harrington, P. J.; Brown, J. D.; Foderano, T.; Hughes, R. C. *Org. Process Res. Dev.* **2004**, *8*, 86.

(60) Garro-Helion, F.; Merzouk, A.; Guibé, F. J. *J. Org. Chem.* **1993**, *58*, 6109.

(61) Abrecht, S.; Karpf, M.; Trussardi, R.; Wirz, B. EP 1127872 A1, 2001; Chem. Abstr. 2001, *135*, 195452.

(62) (a) Zutter, U.; Iding, H.; Wirz, B. EP 1146036 A2, 2001; Chem. Abstr. 2001, *135*, 303728. (b) Zutter, U.; Iding, H.; Spurr, P.; Wirz, B. *J. Org. Chem.* **2008**, *73*, 4895.

(63) Boaz, N. E. *Tetrahedron: Asymmetry* **1999**, *10*, 813.

(64) Yeung, Y.-Y.; Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 6310.

(65) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388.

(66) (a) Knapp, S.; Gibson, F. S. *Organic Synthesis*; Wiley & Sons: New York, 1998; Collect. Vol. IX, pp 516521. (b) Knapp, S.; Levorse, A. T. *J. Org. Chem.* **1988**, *53*, 4006.

(67) Kipassa, N. T.; Okamura, H.; Kina, K.; Hamada, T.; Iwagawa, T. *Org. Lett.* **2008**, *10*, 815.

(68) Posner, H. G.; Vinader, V.; Afarinkia, K. J. *J. Org. Chem.* **1992**, *57*, 4088.

(69) Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353.

(70) Chankeshwara, S. V.; Chakraborti, A. K. *Org. Lett.* **2006**, *8*, 3259.

(71) Okamura, H.; Morishige, K.; Iwagawa, T.; Nakatani, M. *Tetrahedron Lett.* **1998**, *39*, 1211.

(72) Fukuta, Y.; Mita, T.; Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6312.

(73) Mita, T.; Fukuda, N.; Roca, F. X.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2007**, *9*, 259.

(74) Yamatsugu, K.; Kamijo, S.; Suto, Y.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2007**, *48*, 1403.

(75) Yamatsugu, K.; Yin, L.; Kamijo, S.; Kimura, Y.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 1070.

(76) Wiberg, K. B.; Nielsen, S. D. *J. Org. Chem.* **1964**, *29*, 3353.

(77) Barton, D. H. R.; Augy-Dorey, S.; Camara, J.; Dalko, P.; Delaumény, J. M.; Géro, S. D.; Quiclet-Sire, B.; Stütz, P. *Tetrahedron* **1990**, *46*, 215.

(78) Guerin, D. J.; Miller, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2134.

(79) Dalko, P. I.; Langlois, Y. *Tetrahedron Lett.* **1998**, *39*, 2107.

(80) Yamada, S.; Kasai, Y.; Shioiri, T. *Tetrahedron Lett.* **1973**, *14*, 1595.

(81) Harusawa, S.; Yoneda, R.; Kurihara, T.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1984**, *25*, 427.

(82) Kurihara, T.; Miki, M.; Yoneda, R.; Harusawa, S. *Chem. Pharm. Bull.* **1986**, *34*, 2747.

(83) Ho, M.; Chung, J. K. K.; Tang, N. *Tetrahedron Lett.* **1993**, *34*, 6513.

(84) Shangguan, N.; Katukojvala, S.; Greenberg, R.; Williams, L. J. *J. Am. Chem. Soc.* **2003**, *125*, 7754.

(85) Witiak, D. T.; Rotella, D. P.; Filippi, J. A.; Gallucci, J. *J. Med. Chem.* **1987**, *30*, 1327.

(86) Albright, J. D.; Goldman, L. *J. Am. Chem. Soc.* **1967**, *89*, 2416.

(87) Chiral HPLC conditions: Daicel Chiralpak AD-H, 2-propanol/hexane 1/9, flow 0.6 mL/min, detection at 254 nm.

(88) (a) Thadani, A. N.; Stankvic, A. R.; Rawal, V. H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5846. (b) Ward, D. E.; Shen, J. *Org. Lett.* **2007**, *9*, 2843. (c) Usuda, H.; Kuramochi, A.; Kanai, M.; Shibasaki, *Org. Lett.* **2004**, *6*, 4387. (d) Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 9626. (e) Liu, D.; Canales, E.; Corey, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 1498. (f) Sudo, Y.; Shirasaki, D.; Harada, S.; Nishida, A. *J. Am. Chem. Soc.* **2008**, *130*, 12588.

(89) Ligands **223** and **225** are commercially available from Junsei Chemical Co., Ltd.

(90) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203.

(91) (a) Nemoto, H.; Kubota, Y.; Yamamoto, Y. *J. Org. Chem.* **1990**, *55*, 4515. (b) Nemoto, H.; Li, X.; Ma, R.; Suzuki, I.; Shibuya, M. *Tetrahedron Lett.* **2003**, *44*, 73.

(92) Wiktelius, D.; Berts, W.; Jensen, A. J.; Gullbo, J.; Saitton, S.; Csöreghd, I.; Luthman, K. *Tetrahedron* **2006**, *62*, 3600.

(93) Cong, X.; Yao, Z.-J. *J. Org. Chem.* **2006**, *71*, 5365.

(94) (a) Mckillop, A.; Taylor, R. J. K.; Waston, R. J.; Lewis, N. *Synthesis* **1994**, 31. (b) Dondoni, A.; Perrone, P. *Synthesis* **1997**, 527.

(95) Cong, X.; Liao, Q.-J.; Yao, Z.-J. *J. Org. Chem.* **2004**, *69*, 5314.

(96) (a) Chang, Y.-K.; Lee, B.-Y.; Kim, D.-J.; Lee, G. S.; Jean, H. B.; Kim, K. S. *J. Org. Chem.* **2005**, *70*, 3299. (b) Somei, M. *Chem. Pharm. Bull.* **1986**, *34*, 4109.

(97) Cong, X.; Hu, F.; Liu, K.-G.; Liao, Q.-J.; Yao, Z.-J. *J. Org. Chem.* **2005**, *70*, 4514.

(98) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191.

(99) González-Bello, C.; Coggins, J. R.; Hawkins, A. R.; Abell, C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 849.

(100) Wen, S.-J.; Yao, Z.-J. *Org. Lett.* **2004**, *6*, 2721.

(101) (a) Satoh, N.; Akiba, T.; Yokoshima, S.; Fukuyama, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5734. (b) Satoh, N.; Akiba, T.; Yokoshima, S.; Fukuyama, T. *Tetrahedron* **2009**, *65*, 3239.

(102) (a) Fowler, F. W. *J. Org. Chem.* **1972**, *37*, 1321. (b) Sundberg, R. J.; Bloom, J. D. *J. Org. Chem.* **1981**, *46*, 4836.

(103) Enantioselective Diels-Alder reactions of dihydropyridines:(a) Takenaka, N.; Huang, Y.; Rawal, V. H. *Tetrahedron* **2002**, *58*, 8299. (b) Nakano, H.; Tsugawa, N.; Fujita, R. *Tetrahedron Lett.* **2005**, *46*, 5677; diastereoselective reactions of chiral dihydropyridines. (c) Mehmandoust, M.; Marazano, C.; Singh, R.; Gillet, B.; Césario, M.; Fourrey, J.-L.; Das, B. C. *Tetrahedron Lett.* **1988**, *29*, 4423. (d) Marazano, C.; Yannic, S.; Genisson, Y.; Mehmandoust, M.; Das, B. C. *Tetrahedron Lett.* **1990**, *31*, 1995. (e) Matsumura, Y.; Nakamura, Y.; Maki, T.; Onomura, O. *Tetrahedron Lett.* **2000**, *41*, 7685. Diastereoselective Diels−Alder reactions between chiral acrylic acid derivatives and hydropyridines: (f) Kouklovsky, C.; Pouilhès, A.; Langlois, Y. *J. Am. Chem. Soc.* **1990**, *112*, 6672. (g) Campbell, M. M.; Sainsbury, M.; Searle, P. A.; Davies, G. M. *Tetrahedron Lett.* **1992**, *33*, 3181.

(104) (a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243. (b) Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79.

(105) (a) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888. (b) Kraus, G. A.; Taschner, M. *J. Org. Chem.* **1980**, *45*, 1175.

(106) Sakaitani, M.; Hori, K.; Ohfune, Y. *Tetrahedron Lett.* **1988**, *29*, 2983.

(107) Moriarty, R. M.; Chany, C. J., II; Vaid, R. K.; Prakash, O.; Tuladhar, S. M. *J. Org. Chem.* **1993**, *58*, 2478.

(108) Shie, J.-J.; Fang, J.-M.; Wang, S.-Y.; Tsai, K.-C.; Cheng, Y.-S. E.; Yang, A.-S.; Hsiao, S.-C.; Su, C.-Y.; Wong, C.-H. *J. Am. Chem. Soc.* **2007**, *129*, 11892.

(109) Suhara, Y.; Nihei, K.-I.; Kurihara, M.; Kittaka, A.; Yamaguchi, K.; Fujishima, T.; Konno, K.; Miyata, N.; Takayama, H. *J. Org. Chem.* **2001**, *66*, 8760.

(110) Stigers, K. D.; Mar-Tang, R.; Bartlett, P. A. *J. Org. Chem.* **1999**, *64*, 8409.

(111) Shie, J.-J.; Fang, J.-M.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2008**, *47*, 5788.

(112) (a) Boyd, D. R.; Sheldrake, G. N. *Nat. Prod. Rep.* **1998**, *15*, 309. (b) Hudlicky, T.; Gonzalez, D. T.; Gibson, D. T. *Aldrichimica Acta* **1999**, *32*, 35. (c) Endoma, M. A.; Bui, V. P.; Hansen, J.; Hudlicky, T. *Org. Process Res. Dev.* **2002**, *6*, 525. (d) Banwell, M. G.; Edwards, A. J.; Harfoot, G. J.; Jolliffe, K. A.; McLeod, M. D.; McRae, K. J.; Stewart, S. G.; Vögtle, M. *Pure. Appl. Chem.* **2003**, *75*, 223. (e) Johnson, R. A. *Org. React.* **2004**, *63*, 117.

(113) Yeung, Y.-Y.; Gao, X.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 9644.

(114) Blacker, A. J.; Booth, R. J.; Davies, G. M.; Sutherland, J. K. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2861.

(115) Akhlaghinia, B. *Synthesis* **2005**, 1955.

(116) Humphreys, J. L.; Lowes, D. J.; Wesson, K. A.; Whitehead, R. C. *Tetrahedron* **2006**, *62*, 5099.

(117) Bumagin, N. A.; Nikitin, K. V.; Beletskaya, I. P. *J. Organomet. Chem.* **1988**, *358*, 563.

(118) Bromfield, K. M.; Gradén, H.; Hagberg, D. P.; Olsson, T.; Kann, N. *Chem. Commun.* **2007**, 3183.

(119) (a) Pearson, A. J. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: Oxford, 1995; Vol. 12, pp 637−683. (b) Pearson, A. J. *Iron Carbonyl Compounds in Organic Synthesis*; Academia Press: London, 1994.

(120) (a) Pearson, A. J.; Rees, D. C. *J. Am. Chem. Soc.* **1982**, *104*, 1118. (b) Stephenson, G. R.; Owen, D. A. *Tetrahedron Lett.* **1991**, *32*, 1291. (c) Knölker, H. J.; Hopfmann, T. *Synlett* **1995**, 981. (d) Knölker, H. J.; Baum, E.; Hopfmann, T. *Tetrahedron* **1999**, *55*, 10391.

(121) Birch, A. J.; Williamson, D. H. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1892.

(122) (a) Gradén, H.; Hallberg, J.; Kann, N.; Olsson, T. *J. Comb. Chem.* **2004**, *6*, 783. (b) Bohlmann, F.; Zdero, C. *Chem. Ber.* **1973**, *106*, 3779. (c) Himeda, Y.; Yamakata, H.; Ueda, I.; Hatanaka, M. *J. Org. Chem.* **1997**, *62*, 6529.

(123) Birch, A. J.; Bandara, B. M. R. *Tetrahedron Lett.* **1980**, *21*, 2981.

(124) Bandara, B. M. R.; Birch, A. J.; Kelly, L. F. *J. Org. Chem.* **1984**, *49*, 2496.

(125) Franck-Neumann, M.; Heitz, M. P.; Martina, D. *Tetrahedron Lett.* **1983**, *24*, 1615.

(126) Kocovsky, P.; Stary, I. *J. Org. Chem.* **1990**, *55*, 3236.

(127) Trost, B. M.; Zhang, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 3759.

(128) Trost, B. M.; Massiot, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 4405.

(129) (a) Cui, Y.; He, C. *J. Am. Chem. Soc.* **2003**, *125*, 16202. (b) Li, Z.; Ding, X.; He, C. *J. Org. Chem.* **2006**, *71*, 5876.

(130) (a) Guthikonda, K.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, *124*, 13672. (b) Guthikonda, K.; Wehn, P. M.; Caliando, B. J.; Du Bois, J. *Tetrahedron* **2006**, *62*, 11331.

(131) (a) Espino, C. G.; Fiori, K. W.; Kim, J.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378. (b) Fiori, K. W.; Du Bois, J. *J. Am. Chem. Soc.* **2007**, *129*, 562.

(132) Matveenko, M.; Banwell, M. G.; Willis, A. C. *Tetrahedron Lett.* **2008**, *49*, 7018.

(133) Liu, R.; Herron, S. R.; Fleming, S. A. *J. Org. Chem.* **2007**, *72*, 5587, and references therein.

(134) (a) Draths, K. M.; Knop, D. R.; Frost, J. W. *J. Am. Chem. Soc.* **1999**, *121*, 1603. (b) Bogosian, G. WO 2008/128076 A1; CAN: 149: 469520. (c) Pittard, A. J. In *Escherichia coli and Salmonella: Cellular and Molecular Biology*; Neidhardt, F. C., Ed.; ASM Press: Washington, DC, 1996; Chapter 28.

(135) Nie, L.-D.; Shi, X.-X. *Tetrahedron: Asymmetry* **2009**, *20*, 124.

(136) Nie, L.-D.; Shi, X.-X.; Ko, K. H.; Lu, W.-D. *J. Org. Chem.* **2009**, *74*, 3970.

(137) Ishikawa, H.; Suzuki, T.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 1304.

(138) (a) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212. (b) Gotoh, H.; Masui, R.; Ogino, H.; Shoji, M.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 6853. (c) Gotoh, H.; Hayashi, Y. *Org. Lett.* **2007**, *9*, 2859. (d) Hayashi, Y.; Okano, T.; Aratake, S.; Hazelard, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 4922. (e) Gotoh, H.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2007**, *9*, 5307. (f) Hayashi, Y.; Gotoh, H.; Masui, R.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 4012. (g) Hayashi, Y.; Samanta, S.; Gotoh, H.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6634. (h) Hayashi, Y.; Itoh, T.; Ohkubo, M.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 4722. (i) Hayashi, Y.; Okano, T.; Itoh, T.; Urushima, T.; Ishikawa, H.; Uchimaru, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 9053. (j) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794. (k) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjærsgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703. (l) Franke, P. T.; Johansen, R. L.; Bertelsen, S.; Jørgensen, K. A. *Chem. Asian J.* **2008**, *3*, 216.

(139) (a) Naegeli, C.; Tyabji, A. *Helv. Chim. Acta* **1934**, *17*, 931. (b) Barnum, E. R.; Hamilton, C. S. *J. Am. Chem. Soc.* **1942**, *64*, 540. (c) Press, J. B.; Hofmann, C. M.; Safir, S. R. *J. Org. Chem.* **1979**, *44*, 3292.

(140) Mandai, T.; Oshitari, T. *Synlett* **2009**, 783.

(141) Oshitari, T.; Mandai, T. *Synlett* **2009**, 787.

(142) Schmid, C. R.; Bradley, D. A. *Synthesis* **1992**, 587.

(143) (a) Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, 1593. (b) Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1983**, *24*, 4581.

(144) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768.

(145) (a) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559. (b) Anelli, P. L.; Montanari, F.; Quici, S. *Org. Synth.* **1990**, *69*, 212. (c) Leanna, M. R.; Sowin, T. J.; Morton, H. E. *Tetrahedron Lett.* **1992**, *33*, 5029.

(146) (a) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Siret, P.; Keck, G. E.; Gras, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 8031. (b) Snyder, S. A.; Corey, E. J. *Tetrahedron Lett.* **2006**, *47*, 2083.

(147) Osby, J. O.; Martin, M. G.; Ganem, B. *Tetrahedron Lett.* **1984**, *25*, 2093.

(148) Wallace, G. A.; Scott, R. W.; Heathcock, C. H. *J. Org. Chem.* **2000**, *65*, 4145.

(149) (a) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223. (b) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Curr. Med. Chem.* **2004**, *11*, 1837.

(150) (a) Ohfune, Y.; Kurokawa, N. *Tetrahedron Lett.* **1984**, *25*, 1071. (b) Mandai, T.; Matsumoto, S.; Kohama, M.; Kawada, M.; Tsuji, J.; Saito, S.; Moriwake, T. *J. Org. Chem.* **1990**, *55*, 5671.

(151) Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765.

(152) Cuny, G. D.; Buchwald, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 2066.

(153) (a) Billig, E.; Abatjoglou, A. G.; Bryant, D. R. US 4769498, 1988. CAN 111:117287.

(154) The synthetic routes included in this review were reported before May 4, 2009, according to the results of a SciFinder literature search carried out on this date.

(155) For information on a recent settlement between Biota and GSK on the commercialization of zanamivir, see:(a) http://www.theaustralian.news.com.au, July 21, 2008;(b) http://www.businessspectator-.com.au, July 21, 2008..

(156) Andraos, J. *Org. Process Res. Dev.* **2009**, *13*, 161.

(157) Hileman, B. *Chem. Eng. News* **2005**, *83*, 47.

(158) While this manuscript was being finalized, an outbreak of H1N1 swine flu had taken place in Mexico and was quickly spreading around the world. The World Health Organization had raised the alert level due to fears that it might turn into a global pandemic.

(159) For information on the resistance of influenza viruses to neuraminidase inhibitors, see:(a) McKimm-Breschkin, J. L. *Antiviral Res.* **2000**, *47*, 1. (b) Moscona, A. *N. Engl. J. Med.* **2005**, *353*, 2633. (c) de Jong, M. D.; Thanh, T. T.; Khanh, T. H.; Hien, V. M.; Smith, G. J. D.; Chau, N. V.; Cam, B. V.; Qui, P. T.; Ha, D.; Guan, Y.; Peiris, J. S. M.; Hien, T. T.; Farrar, J. *N. Engl. J. Med.* **2005**, *353*, 2667. (d) Lackenby, A.; Thompson, C.; Democratis, J. *Curr. Opin. Infect. Dis.* **2008**, *21*, 626. (e) García-Sosa, A. T.; Sild, S.; Maran, U. *J. Chem. Inf. Model.* **2008**, *48*, 2074. (f) Collins, P. J.; Haire, L. F.; Lin, Y. P.; Liu, J.; Russell, R. J.; Walker, P. A.; Skehel, J. J.; Martin, S. R.; Hay, A. J.; Gamblin, S. J. *Nature* **2008**, *453*, 1258. (g) Mihajlovic, M. L.; Mitrasinovic, P. M. *Biophys. Chem.* **2008**, *136*, 152. (h) Hill, A. W.; Guralnick, R. P.; Wilson, M. J. C.; Habib, F.; Janies, D. *Infect. Genet. Evol.* **2009**, *9*, 169. (i) Moscona, A. *N. Engl. J. Med.* **2009**, *360*, 953.

(160) (a) Zhang, J.; Xu, W.; Liu, A.; Du, G. *Med. Chem.* **2008**, *4*, 206. (b) Zhang, J.; Wang, Q.; Fang, H.; Xu, W.; Liu, A.; Du, G. *Bioorg. Med. Chem.* **2008**, *16*, 3839. (c) Miki, K.; Nagai, T.; Nakamura, T.; Tuji, M.; Koyama, K.; Kinoshita, K.; Furuhata, K.; Yamada, H.; Takahashi, K. *Heterocycles* **2008**, *75*, 879. (d) Krueger, A. C.; Xu, Y.; Kati, W. M.; Kempf, D. J.; Maring, C. J.; McDaniel, K. F.; Molla, A.; Montgomery, D.; Kohlbrenner, W. E. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1692. (e) Szabo, Z. B.; Borbas, A.; Bajza, I.; Liptak, A.; Antus, S. *Tetrahedron Lett.* **2008**, *49*, 1196. (f) Magesh, S.; Moriya, S.; Suzuki, T.; Miyagi, T.; Ishida, H.; Kiso, M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 532. (g) Liu, Z.-Y.; Wang, X.; Zhao, L.-X.; Li, Y.-H.; Shao, H.-Y.; Yi, H.; You, X.-F.; Li, Z.-R. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4851. (h) Lu, Y.; Gervay-Hague, J. *Carbohydr. Res.* **2007**, *342*, 1636. (i) Ye, D.; Li, J.; Zhang, J.; Liu, H.; Jiang, H. *Tetrahedron Lett.* **2007**, *48*, 4023. (j) Sato, K.; Ikeda, K.; Suzuki, T.; Aoyama, S.; Maki, N.; Suzuki, T.; Sato, M. *Tetrahedron* **2007**, *63*, 7571. (k) Matsuoka, K.; Takita, C.; Koyama, T.; Miyamoto, D.; Yingsakmongkon, S.; Hidari, K. I. P. J.; Jampangern, W.; Suzuki, T.; Suzuki, Y.; Hatano, K.; Terunuma, D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3826. (l) Shie, J.-J.; Fang, J.-M.; Wang, S.-Y.; Tsai, K.-

C.; Cheng, Y.-S. E.; Yang, A.-S.; Hsiao, S.-C.; Su, C.-Y.; Wong, C.-H. *J. Am. Chem. Soc.* **2007**, *129*, 11892. (m) Zhang, J.; Wang, Q.; Fang, H.; Xu, W.; Liu, A.; Du, G. *Bioorg. Med. Chem.* **2007**, *15*, 2749. (n) Tindal, D. J.; Dyason, J. C.; Thomson, R. J.; Suzuki, T.; Ueyama, H.; Kuwahara, Y.; Maki, N.; Suzuki, Y.; von Itzstein, M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1655. (o) Hu, F.; Zhang, Y.-H.; Yao, Z.-J. *Tetrahedron Lett.* **2007**, *48*, 3511. (p) Kraus, G. A.; Goronga, T. *Synthesis* **2007**, 1765. (q) Li, J.; Zheng, M.; Tang, W.; He, P.-L.; Zhu, W.; Li, T.; Zuo, J.-P.; Liu, H.; Jiang, H. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5009. (r) Sun, C.; Zhang, X.; Huang, H.; Zhou, P. *Bioorg. Med. Chem.* **2006**, *14*, 8574. (s) Ikeda, K.; Sato, K.; Kitani, S.; Suzuki, T.; Maki, N.; Suzuki, Y.; Sato, M. *Bioorg. Med. Chem.* **2006**, *14*, 7893. (t) Laver, G. *Fut. Virol.* **2006**, *1*, 577. (u) Streicher, H.; Busse, H. *Bioorg. Med. Chem.* **2006**, *14*, 1047. (v) Chand, P.; Bantia, S.; Kotian, P. L.; El-Kattan, Y.; Lin, T.-H.; Babu, Y. S. *Bioorg. Med. Chem.* **2005**, *13*, 4071. (w) Maring, C. J.; Stoll, V. S.; Zhao, C.; Sun, M.; Krueger, A. C.; Stewart, K. D.; Madigan, D. L.; Kati, W. M.; Xu, Y.; Carrick, R. J.; Montgomery, D. A.; Kempf-Grote, A.; Marsh, K. C.; Molla, A.; Steffy, K. R.; Sham, H. L.; Laver, W. G.; Gu, Y.-G.; Kempf, D. J.; Kohlbrenner, W. E. *J. Med. Chem.* **2005**, *48*, 3980. (x) Chand, P.; Kotian, P. L.; Morris, P. E.; Bantia, S.; Walsh, D. A.; Babu, Y. S. *Bioorg. Med. Chem.* **2005**, *13*, 2665. (y) Bianco, A.; Brufani, M.; Dri, D. A.; Melchioni, C.; Filocamo, L. *Lett. Org. Chem.* **2005**, *2*, 83. (z) Wang, G. T.; Wang, S.; Gentles, R.; Sowin, T.; Maring, C. J.; Kempf, D. J.; Kati, W. M.; Stoll, V.; Stewart, K. D.; Laver, G. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 125. (aa) MacDonald, S. J. F.; Cameron, R.; Demaine, D. A.; Fenton, R. J.; Foster, G.; Gower, D.; Hamblin, J. N.; Hamilton, S.; Hart, G. J.; Hill, A. P.; Inglis, G. G. A.; Jin, B.; Jones, H. T.; McConnell, D. B.; McKimm-Breschkin, J.; Mills, G.; Nguyen, V.; Owens, I. J.; Parry, N.; Shanahan, S. E.; Smith, D.; Watson, K. G.; Wu, W.-Y.; Tucker, S. P. *J. Med. Chem.* **2005**, *48*, 2964. (ab) Gonzalez-Diaz, H.; Cruz-Monteagudo, M.; Vina, D.; Santana, L.; Uriarte, E.; De Clercq, E. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1651. (ac) Liu, K.-G.; Yan, S.; Wu, Y.-L.; Yao, Z.-J. *Org. Lett.* **2004**, *6*, 2269. (ad) Watson, K. G.; Cameron, R.; Fenton, R. J.; Gower, D.; Hamilton, S.; Jin, B.; Krippner, G. Y.; Luttick, A.; McConnell, D.; MacDonald, S. J. F.; Mason, A. M.; Nguyen, V.; Tucker, S. P.; Wu, W.-Y. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1589. (ae) Mann, M. C.; Thomson, R. J.; von Itzstein, M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5555. (af) Chand, P.; Babu, Y. S.; Bantia, S.; Rowland, S.; Dehghani, A.; Kotian, P. L.; Hutchison, T. L.; Ali, S.; Brouillette, W.; El-Kattan, Y.; Lin, T.-H. *J. Med. Chem.* **2004**, *47*, 1919. (ag) Streicher, H. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 361. (ah) Li, L.-S.; Wu, Y.-L. *Curr. Org. Chem.* **2003**, *7*, 447. (ai) Stoll, V.; Stewart, K. D.; Maring, C. J.; Muchmore, S.; Giranda, V.; Gu, Y. Y.; Wang, G.; Chen, Y.; Sun, M.; Zhao, C.; Kennedy, A. L.; Madigan, D. L.; Xu, Y.; Saldivar, A.; Kati, W.; Laver, G.; Sowin, T.; Sham, H. L.; Greer, J.; Kempf, D. *Biochemistry* **2003**, *42*, 718. (aj) Masuda, T.; Shibuya, S.; Arai, M.; Yoshida, S.; Tomozawa, T.; Ohno, A.; Yamashita, M.; Honda, T. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 669. (ak) Masuda, T.; Yoshida, S.; Arai, M.; Kaneko, S.; Yamashita, M.; Honda, T. *Chem. Pharm. Bull.* **2003**, *51*, 1386. (al) Barnes, D. M.; Bhagavatula, L.; DeMattei, J.; Gupta, A.; Hill, D. R.; Manna, S.; McLaughlin, M. A.; Nichols, P.; Premchandran, R.; Rasmussen, M. W.; Tian, Z.; Wittenberger, S. J. *Tetrahedron: Asymmetry* **2003**, *14*, 3541. (am) Sasaki, K.; Nishida, Y.; Uzawa, H.; Kobayashi, K. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2821. (an) Masuda, T.; Shibuya, S.; Arai, M.; Yoshida, S.; Tomozawa, T.; Ohno, A.; Yamashita, M.; Honda, T. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 669. (ao) Mineno, T.; Miller, M. J. *J. Org. Chem.* **2003**, *68*, 6591. (ap) Hochguertel, M.; Biesinger, R.; Kroth, H.; Piecha, D.; Hofmann, M. W.; Krause, S.; Schaaf, O.; Nicolau, C.; Eliseev, A. V. *J. Med. Chem.* **2003**, *46*, 356. (aq) Honda, T.; Masuda, T.; Yoshida, S.; Arai, M.; Kobayashi, Y.; Yamashita, M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1921. (ar) Honda, T.; Masuda, T.; Yoshida, S.; Arai, M.; Kaneko, S.; Yamashita, M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1925. (as) Honda, T.; Yoshida, S.; Arai, M.; Masuda, T.; Yamashita, M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1929. (at) Hanessian, S.; Wang, J.; Montgomery, D.; Stoll, V.; Stewart, K. D.; Kati, W.; Maring, C.; Kempf, D.; Hutchins, C.; Laver, W. G. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3425. (au) DeGoey, D. A.; Chen, H.-J.; Flosi, W. J.; Grampovnik, D. J.; Yeung, C. M.; Klein, L. L.; Kempf, D. J. *J. Org. Chem.* **2002**, *67*, 5445. (av) Streicher, H.; Bohner, C. *Tetrahedron* **2002**, *58*, 7573. (aw) Hanessian, S.; Bayrakdarian, M.; Luo, X. *J. Am. Chem. Soc.* **2002**, *124*, 4716. (ax) Barnes, D. M.; McLaughlin, M. A.; Oie, T.; Rasmussen, M. W.; Stewart, K. D.; Wittenberger, S. J. *Org. Lett.* **2002**, *4*, 1427. (ay) Wyatt, P. G.; Coomber, B. A.; Evans, D. N.; Jack, T. I.; Fulton, H. E.; Wonacott, A. J.; Colman, P.; Varghese, J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 669. (az) Kerrigan, S. A.; Pritchard, R. G.; Smith, P. W.; Stoodley, R. J. *Tetrahedron Lett.* **2001**, *42*, 8889. (ba) Chand, P.; Kotian, P. L.; Dehghani, A.; El-Kattan, Y.; Lin, T.-H.; Hutchison, T. L.; Babu, Y. S.; Bantia, S.; Elliott, A. J.; Montgomery, J. A. *J. Med. Chem.* **2001**, *44*, 4379. (bb) Kerrigan, S. A.; Pritchard, R. G.; Smith, P. W.; Stoodley, R. J. *Tetrahedron Lett.* **2001**, *42*, 7687. (bc) Bianco, A.; Brufani, M.; Manna, F.; Melchioni, C. *Carbohydr. Res.* **2001**, *332*, 23. (bd) Wang, G. T.; Chen, Y.; Wang, S.; Gentles, R.; Sowin, T.; Kati, W.; Muchmore, S.; Giranda, V.; Stewart, K.; Sham, H.; Kempf, D.; Laver, W. G. *J. Med. Chem.* **2001**, *44*, 1192. (be) McNicholl, I. R.; McNicholl, J. J. *Ann. Pharmacother.* **2001**, *35*, 57. (bf) Shitara, E.; Nishimura, Y.; Nerome, K.; Hiramoto, Y.; Takeuchi, T. *Org. Lett.* **2000**, *2*, 3837. (bg) Knapp, S.; Zhao, D. *Org. Lett.* **2000**, *2*, 4037. (bh) Babu, Y. S.; Chand, P.; Bantia, S.; Kotian, P.; Dehghani, A.; El-Kattan, Y.; Lin, T.-H.; Hutchison, T. L.; Elliott, A. J.; Parker, C. D.; Ananth, S. L.; Horn, L. L.; Laver, G. W.; Montgomery, J. A. *J. Med. Chem.* **2000**, *43*, 3482. (bi) Sun, X.-L.; Kanie, Y.; Guo, C.-T.; Kanie, O.; Suzuki, Y.; Wong, C.-H. *Eur. J. Org. Chem.* **2000**, 2643. (bj) Lew, W.; Wu, H.; Chen, X.; Graves, B. J.; Escarpe, P. A.; MacArthur, H. L.; Mendel, D. B.; Kim, C. U. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1257. (bk) Wang, Q.; Wolff, M.; Polat, T.; Du, Y.; Linhardt, R. J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 941. (bl) Sorbera, L. A.; Graul, A.; Castaner, J. *Drugs Fut.* **2000**, *25*, 249. (bm) Andrews, D. M.; Cherry, P. C.; Humber, D. C.; Jones, P. S.; Keeling, S. P.; Martin, P. F.; Shaw, C. D.; Swanson, S. *Eur. J. Med. Chem.* **1999**, *34*, 563. (bn) Zhang, L.; Williams, M. A.; Mendel, D. B.; Escarpe, P. A.; Chen, X.; Wang, K.-Y.; Graves, B. J.; Lawton, G.; Kim, C. U. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1751. (bo) Kiefel, M. J.; von Itzstein, M. *Prog. Med. Chem.* **1999**, *36*, 1. (bp) Smith, P. W.; Robinson, J. E.; Evans, D. N.; Sollis, S. L.; Howes, P. D.; Trivedi, N.; Bethell, R. C. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 601. (bq) Kim, C. U.; Lew, W.; Williams, M. A.; Wu, H.; Zhang, L.; Chen, X.; Escarpe, P. A.; Mendel, D. B.; Laver, W. G.; Stevens, R. C. *J. Med. Chem.* **1998**, *41*, 2451. (br) Smith, P. W.; Sollis, S. L.; Howes, P. D.; Cherry, P. C.; Starkey, I. D.; Cobley, K. N.; Weston, H.; Scicinski, J.; Merritt, A.; Whittington, A.; Wyatt, P.; Taylor, N.; Green, D.; Bethell, R.; Madar, S.; Fenton, R. J.; Morley, P. J.; Pateman, T.; Beresford, A. *J. Med. Chem.* **1998**, *41*, 787. (bs) Chand, P.; Babu, Y. S.; Bantia, S.; Chu, N.; Cole, L. B.; Kotian, P. L.; Laver, W. G.; Montgomery, J. A.; Pathak, V. P.; Petty, S. L.; Shrout, D. P.; Walsh, D. A.; Walsh, G. M. *J. Med. Chem.* **1997**, *40*, 4030. (bt) Lew, W.; Williams, M. A.; Mendel, D. B.; Escarpe, P. A.; Kim, C. U. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1843. (bu) Kim, C. U.; Lew, W.; Williams, M. A.; Zhang, L.; Liu, H.; Swaminathan, S.; Bischofberger, N.; Chen, M. S.; Tai, C. Y.; Mendel, D. B.; Laver, W. G.; Stevens, R. C. *J. Am. Chem. Soc.* **1997**, *119*, 681. (bv) Fromtling, R. A.; Castaner, J. *Drugs Fut.* **1996**, *21*, 375. (bw) Kok, G. B.; Campbell, M.; Mickey, B.; von Itzstein, M. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2811. (bx) Howes, P. D.; Smith, P. W. *Tetrahedron Lett.* **1996**, *37*, 6595. (by) Smith, P. W.; Starkey, I. D.; Howes, P. D.; Sollis, S. L.; Keeling, S. P.; Cherry, P. C.; von Itzstein, M.; Wu, W. Y.; Jin, B. *Eur. J. Med. Chem.* **1996**, *31*, 143. (bz) Chandler, M.; Conroy, R.; Cooper, A. W. J.; Lamont, R. B.; Scicinski, J. J.; Smart, J. E.; Storer, R.; Wier, N. G.; Wilson, R. D.; Wyatt, P. G. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1189. (ca) Bamford, M. J.; Pichel, J. C.; Husman, W.; Patel, B.; Storer, R.; Wier, N. G. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1181.

(161) Abbott, A. *Nature* **2005**, *435*, 407.

(162) See http://www.roche.com/med-cor-2006-04-19.

(163) During the galley proofing of this manuscript, a new synthesis of oseltamivir has appeared in the literature: Sullivan, B.; Carrera, I.; Drouin, M.; Hudlicky, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 4229.

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